Validating Controlled Substances

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Disclosure

All authors have no financial relationships to disclose with regards to this presentation.

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Objectives

- Discuss the laws and regulations related to the prescribing and dispensing of controlled substances
- Review the role and appropriateness of opioids in the treatment of acute and chronic pain management
- Identify methods for validating controlled substance prescriptions and review strategies for distinguishing invalid prescriptions
- Review Florida's Prescription Drug Monitoring Program's Database (PDMP)
- Review patient counseling points for controlled substances including adverse effects, drug interactions, storage conditions, and disposal
- Explain the use of naloxone for the emergency treatment of suspected drug overdose and review the treatment resources for opioid physical dependence, addiction, misuse, and abuse

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Background

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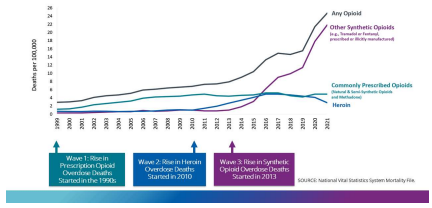
US Opioid Crisis

Three Waves of Opioid Overdose Deaths



CDC, 2023

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US Opioid Statistics

- From 1999 to 2021, nearly 645,000 people died from an opioid overdose, including prescription and non-prescription opioids
- Over 75% of the nearly 107,000 drug overdose deaths in 2021 involved an opioid

6-fold the number in 1999

CDC, 2023

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Role of Opioids in Pain

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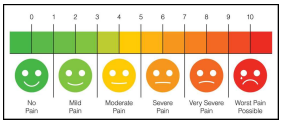
Pain

- Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage"
- Scales
  - Numerical Pain Rating Scale
  - Wong-Baker FACES® Pain Rating Scale



Raja et al., 2020

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Characteristics of Pain

Two primary pathways of pain

Nociceptive

- Aching
- Sharp
- Throbbing
- Usually localized

Neuropathic

- Burning
- Radiating
- Shock-like
- Tingling/numbness

Raja et al., 2020

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Acute vs Non-acute/Chronic Pain

	Acute Pain	Non-acute/Chronic Pain
Definition	Normal, predicted, physiological, and time-limited response to an adverse chemical, thermal, or mechanical stimulus	Malignancy, terminal condition, palliative care or serious traumatic injury with an Injury Severity Score (ISS) ≥ 9 Chronic nonmalignant pain persisting for > 90 days
Treatment goal	**Cure**	**Functionality**
Dependence and Tolerance	Unusual	Common
Symptoms	Anxiety, tachycardia, tachypnea, hypertension, diaphoresis, dilated pupils	Depressed mood, fatigue, lack of motivation, loss of appetite, loss of libido

Raja et al., 2020

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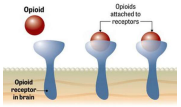
Opioids

Mechanism
- Agonist of opioid receptors (mu, kappa, and delta) → inhibition of ascending pain pathway

Administration
- Oral, intravenous, intramuscular, subcutaneous, sublingual, rectal, intranasal, and transdermal patch

Adverse reactions
- Nausea and vomiting, constipation, dizziness, somnolence, pruritus, flushing, reduced respiratory rate

Warnings
- Risk evaluation and mitigation strategy (REMS) approved on July 9, 2012



Opioids can cause **DEPENDENCE, ADDICTION** and **OVERDOSE.**

Raja et al., 2020

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Laws and Regulations

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The Controlled Substances Act

- The Controlled Substances Act (CSA) is a federal law that regulates certain drugs that are known to have a potential risk of abuse or dependence
- The Drug Enforcement Administration (DEA) was established in 1973 as the primary federal agency responsible for implementing and enforcing the CSA
- The CSA aims to ensure that patients have access to controlled substances for **legitimate** medical purposes while protecting patients against illegitimate use

Controlled Substances Act, 2023

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Controlled Substances Schedule

Schedule	Medical Use	Abuse Potential	Examples
I	No	High	Cannabis, Heroin
II	Yes	High	Fentanyl, Amphetamine
III	Yes	Less than Schedule I or II	Ketamine, Testosterone
IV	Yes	Low	Tramadol, Clonazepam
V	Yes	Low	Pregabalin, Lacosamide

DEA Pharmacist's Manual, 2022

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State Law vs. Federal Law

- Stricter law prevails
- State law can be **more restrictive** than federal law but not less restrictive

Acetaminophen-butalbital-caffeine is classified as a Schedule III in Florida, but it is not classified as a controlled substance by the Food and Drug Administration (FDA)

- It is our responsibility as pharmacists to stay up to date

Chapter 465, 2023

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What is our role?

- Dispense medication if issued for a legitimate medical purpose
- Refuse to fill a medication for a prescription of questionable or suspicious medical legitimacy
- Encourage patients to review the effectiveness and safety of their therapeutic regimen with prescribers

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Controlled Substance Prescription Process

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Valid Prescription

Valid prescription	• Issued for a legitimate medical purpose by a practitioner acting in the scope of professional practice maintaining a practitioner-patient relationship
Invalid prescription	• Not issued in compliance with the definition of a valid prescription

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Valid Prescription Requirements

Patient Information	Prescriber Information	Drug Information	Prescription Information
• Full name • Address	• Full name • Address • DEA number • Signature	• Name • Strength • Dosage form • Quantity (numerical and written) • Directions for use • Refills (if applicable)	• Issue date

DEA Pharmacist's Manual, 2022

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Knowledge Check

Which of the following elements are NOT required in a controlled substance prescription?

a. Patient's address

b. Prescriber's NPI

c. Prescriber's address

d. Date prescribed

e. Drug quantity written

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DEA Number Calculation

- A valid DEA number contains two letters, six numbers, and one check digit (Example: AM1234563)
- The first letter is a code identifying type of registrant
- The second letter is the first letter of the prescriber's last name
- Calculation (confirm veracity of DEA number with one check digit)
  - Step 1: Add 1st, 3rd, and 5th digits
  - Step 2: Add 2nd, 4th, and 6th digits and multiply sum by 2
  - Step 3: Calculate the sum of steps 1 and 2
  - Step 4: The last digit of the sum should correspond to the last digit of the DEA number

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DEA Number Calculation

- Example: AM1234563 → John Myers, MD
- Calculation (confirm veracity of DEA number with one check digit)
  - Step 1: Add 1st, 3rd, and 5th digits
    1 + 3 + 5 = 9
  - Step 2: Add 2nd, 4th, and 6th digits and multiply sum by 2
    2 + 4 + 6 = 12 x 2 = 24
  - Step 3: Calculate the sum of steps 1 and 2
    9 + 24 = 33
  - Step 4: The last digit of the sum should correspond to the last digit of the DEA number
    3 = 3

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Registrant Types

First letter of the DEA number

- A/B/F – Hospital/Clinic/Practitioner/Pharmacy/Teaching Institution
- G – Department of Defense Contractors
- M – Mid-level Practitioner (NP/PA/OD/ET, etc.)
- P/R – Manufacturer/Distributor/Researcher/Analytical Lab/Importer/Exporter/Reverse Distributor/Narcotic Treatment Program

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Knowledge Check

A patient drops off a controlled substance prescription at your pharmacy. You want to review if the DEA number provided in the prescription is valid: Lily Sanders, MD *AD3421908.* Would you accept the script?

a. Yes

b. No

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Receiving a Prescription

What shall **not** be changed?

- Patient name
- Drug name
- Prescriber name and signature

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Accepted Prescriptions

- Electronic prescriptions are **mandatory** in Florida
  - Florida passed legislation in 2019 requiring that healthcare practitioners issue all prescriptions, including controlled substance prescriptions, **electronically**
  - Law only applies to healthcare practitioners who maintain a system of electronic health records

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Accepted Prescriptions

Electronic prescriptions are **not required** if

- Prescription is issued to an individual receiving hospice care or who is a resident of a nursing home
- Practitioner determines that it is in the best interest of the patient, or the patient determines that it is in his/her best interest
- Drug under a research protocol
- Practitioner determines that it would be impractical for the patient to obtain the drug by electronic prescription in a timely manner and such delay would adversely impact patient's medical condition
- Practitioner and dispenser are the same entity
- Practitioner has been issued a waiver due to technology limitations

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Refills of Controlled Substances

Schedule II

- **Not** allowed
- A new prescription is required per fill
  - Prescriber may issue multiple prescriptions up to a 90-day supply

Schedule III-V

- **Up to five times within six months** after the issue date
- After five refills or after six months, whichever occurs first, a new prescription will be required

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Partial Fills of Controlled Substances

- Partial fills are **not** considered a refill
- Must ensure the total quantity dispensed does not exceed the quantity prescribed

Schedule II

- Within 30 days from the issue date of the prescription if requested by a patient or a prescriber
- Within 60 days from the issue date of the prescription for either terminally ill patients or patients in long-term care facility or nursing homes

Schedule III-V

- Within 6 months from the issue date of the prescription

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Emergency Exceptions

State of emergency declared by Governor allows a 30-day supply if

- Prescription is **not** a Schedule II controlled substance
- The medication is essential to the maintenance of life or to the continuation of therapy in a chronic condition
- In the pharmacist's professional judgment, the interruption of therapy might produce undesirable health consequences
- The pharmacist creates a written order containing all the prescription information requirements
- The pharmacist notifies the prescriber of the emergency dispensing within a reasonable time after such dispensing

Other emergency situations allows a 72-hour supply if

- Verbal prescriptions with Schedule II (signed or electronic prescription should be provided to pharmacy within 7 days)
- Refills for Schedule III-V

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Transfers of Controlled Substances

Unfilled prescriptions with **Schedule II-V** controlled substances

- May transfer if pharmacies share an electronic, real-time, online database

Refills of **Schedule III-V** controlled substances

- May transfer **one time** to another pharmacy
- May transfer **up to the maximum number of refills** permitted by law and the prescriber if pharmacies share an electronic, real-time, online database

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Validating a Prescription

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Validating a Prescription

Every patient's situation is unique

Prescriptions for controlled substances shall be reviewed individually

Pharmacists shall attempt to work with the patient and the prescriber to assist in determining the validity of the prescription

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Methods for Validating

- Therapeutic Legitimacy
- Visual Authenticity
- Drug Utilization Review (DUR)
- Prescription Drug Monitoring Program (PDMP)

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Therapeutic Legitimacy

Acute Pain

- Schedule II opioids are limited to 3 days
- Supply may be increased to 7 days if determined to be medically necessary and prescriber must add "ACUTE PAIN EXCEPTION" on the prescription
- Schedule II opioids are limited to 14 days for post-surgical procedure

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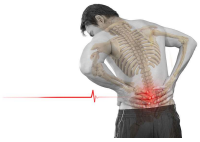
Therapeutic Legitimacy

Non-acute/Chronic Pain

- Prescriber must indicate "NONACUTE PAIN" on the prescription for Schedule II opioids
- Patients treated for a traumatic injury with an ISS greater than or equal to 9 must be concurrently prescribed an emergency opioid antagonist
- If this is not received, pharmacist should follow standard policy and procedures and contact prescriber



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Visual Authenticity

Prescription A	Prescription B
	

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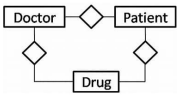
Drug Utilization Review (DUR)

- This is a structured, ongoing, systematic review to ensure the effective and appropriate use of drugs
- **Pharmacists** play a key role
  - Prevent inappropriate therapies
  - Prevent adverse drug reactions
  - Improve overall effectiveness



Carver et al., 2023

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Drug Utilization Review (DUR)

Before dispensing	During dispensing	After dispensing
Abuse and misuse	Interactions	Use, abuse and misuse
Contraindications	Precautions	Duration of treatment
Precautions	Therapeutic interchange	Contraindications
Interactions	Over and under utilization	Duplications
Substitutions		Over and under utilization
Duration of treatment		

Carver et al., 2023

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Drug Utilization Review (DUR)

Drug Class	Interaction with Opioids
Sedative hypnotics (e.g., benzodiazepines, barbiturates)	• ↑ Respiratory depression
Antipsychotic agents & relaxants (e.g., clozapine, cyclobenzaprine)	• ↑ Sedation • ↑ Cardiovascular effects • ↑ or ↓ Respiratory depression
Antidepressant agents (e.g., duloxetine, sertraline)	• Enhance the toxicity of antidepressants

UpToDate, 2024

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Prescription Drug Monitoring Program (PDMP)

- PDMP is an electronic database that tracks the controlled substance prescriptions in each state
- E-FORCSE® (Electronic-Florida Online Reporting of Controlled Substance Evaluation Program) was created by the 2009 Florida Legislature
- Pharmacists are required to check the patient's profile for each new prescription and refill they dispense

E-FORCSE Electronic-Florida Online Reporting of Controlled Substances Evaluation

Florida Health, 2024

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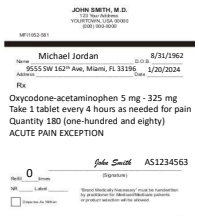
Knowledge Check

You receive the following prescription:

Would you dispense this prescription without clarification from prescriber?

a. Yes

b. No


JOHN SMITH, M.D.
123 Your Address
YOUR CITY, FL 33000
(000) 000-0000

Michael Jordan 8/31/1962
9555 SW 162nd Ave, Miami, FL 33196 1/20/2024

Rx

Oxycodone-acetaminophen 5 mg - 325 mg
Take 1 tablet every 4 hours as needed for pain
Quantity 180 (one-hundred and eighty)
ACUTE PAIN EXCEPTION

John Smith AS1234563

0

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Steps to Validate a Prescription

When validating a controlled substance prescription, we must ensure:

- Prescription has all legally required information
- Prescription looks valid
- Drug, strength, directions, and quantity are appropriate
- Check patient profile
- Check PDMP
- Contact provider, if needed
- Document any change and counsel patients

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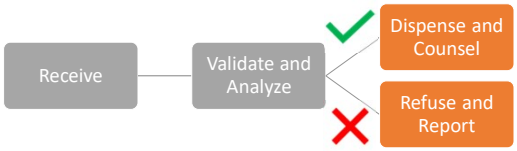
Controlled Substance Prescription Process



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Unbiased Decision-Making

- Do not stereotype patients
- Do not let bad experiences with patients/prescribers dictate how you react in your future interactions
- Do not refuse dispensing controlled substance prescriptions "just because" it is a controlled substance

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Red Flags

- Early fills
- Cash payments
- Filling controlled substances and not filling non-controlled substance
- Patient travelling long distances to fill prescriptions for a controlled substance
- Physician office staff does not allow you to talk to the prescriber directly
- Multiple patients presenting to fill same medications from same doctor
- "Drug cocktails": opioid, benzodiazepine, stimulant
- Altered prescriptions (different handwriting, multiple ink colors)

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Refusing a Prescription

Communicate with

- Patient or representative
- Prescriber or agent

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Tips for Communicating with Prescribers

Introduce yourself

Explain reason of your call

Have prescription and patient information readily available

Address your concerns

Be polite, concise, and assertive

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Duty to Report

- If a pharmacist has reason to believe that a prescriber is involved in drug diversion of controlled substances, the pharmacist is **required to report** the prescriber to the Department of Health
- The report must be made **within 24 hours** after learning of the fraud or at the close of the next business day, whichever is late

https://www.flhealthcomplaint.gov/home

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Tips for your Team

- Have your staff be familiar with the opioid crisis and laws
- Train your team to exercise their right to refuse dispensation of an opioid prescription based upon **reasonable suspicion**
- Have a valid reason when refusing a prescription
- Have great communication skills, especially with your team
- Remember that drug seekers map out pharmacies where communication and cooperation between health professionals is minimal

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Take Home Points

- Opioids are greatly used for pain management
- It is important to complete a meticulous revision when receiving a controlled substance prescription
- Our responsibility is to make sure that all medications are prescribed for legitimate medical purposes, especially controlled substances
- We have a duty to report any prescriber involved in fraud

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Thank you

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Prescription Drug Monitoring Program (PDMP)

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Prescription Drug Monitoring Program (PDMP)

- PDMP is an electronic database that tracks controlled substance prescriptions in a state
- The purpose of the PDMP is to provide the information collected in the database to healthcare practitioners to guide decisions in prescribing and dispensing these highly abused prescription drugs
- It aids pharmacists in making a clinical judgement on whether to dispense or not a controlled substance (CS) prescription, but this decision should not be based solely in PDMP information

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Prescription Drug Monitoring Program (PDMP)

- Electronic-Florida Online Reporting of Controlled Substance Evaluation Program (E-FORSCE™) is Florida's PDMP, and it is run by the Florida Department of Health
- Florida Law requires pharmacists to consult E-FORSCE™ prior dispensing any new or refilled controlled substance prescription
- E-FORSCE™ allows pharmacists to search the patient's controlled substance use in most other states
- Prescribers are required to access and consult the PDMP each time a controlled substance is prescribed or dispensed

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Prescription Drug Monitoring Program (PDMP)

- Consulting the PDMP is **not** required:
  - Patient is less than 16 years old
  - Drug being prescribed is a nonopioid schedule V
  - System is nonfunctional due to operational/technological or electrical failure
- Document in the patient record reason why PDMP could not be accessed, and no more than a 3-day supply can be dispensed
- If you check the PDMP on behalf a physician for whom you are not a designee, Florida's law requirements would not be met until the physician, or their designee check the PDMP again

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Prescription Drug Monitoring Program (PDMP)

Information available within PDMP:

- Drug name, strength, quantity prescribed, and days supply
- Date issued, date filled, and refills ordered
- Prescriber's name, address, DEA number, and NPI
- Patient's name, address, telephone number, and date of birth
- Dispensing pharmacy's name, address, DEA number, and pharmacy permit number
- Methods of payment

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Prescription Drug Monitoring Program (PDMP)

https://florida.pmpaware.net/login

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Prescription Drug Monitoring Program (PDMP)

Filled	Written	Sold	ID	Drug	QTY	Days	Prescriber	RX #	Dispenser	Refill	Daily Dose*	Pymt Type	PMP
12/26/2023	12/21/2023	12/26/2023	2	Clonazepam 0.5 Mg Tablet	30.00	30	Jo Do	412346	Bap	0/3	1.00 LME	Medicaid	FL
07/30/2023	04/04/2023	07/31/2023	1	Clonazepam 0.5 Mg Tablet	30.00	30	Jo Do	412345	Bap	3/3	1.00 LME	Medicaid	FL
06/29/2023	04/04/2023	06/30/2023	1	Clonazepam 0.5 Mg Tablet	30.00	30	Jo Do	412345	Bap	2/3	1.00 LME	Medicaid	FL
05/13/2023	04/04/2023	05/19/2023	1	Clonazepam 0.5 Mg Tablet	30.00	30	Jo Do	412345	Bap	1/3	1.00 LME	Medicaid	FL
04/05/2023	04/04/2023	04/05/2023	1	Clonazepam 0.5 Mg Tablet	30.00	30	Jo Do	412345	Bap	0/3	1.00 LME	Medicaid	FL
05/20/2022	05/20/2022	05/20/2022	2	Oxycodone Hcl (Ir) 5 Mg Tablet	12.00	3	Jo Do	212345	Bap	0/0	30.00 MME	Medicaid	FL
03/07/2022	09/28/2021	03/07/2022	1	Clonazepam 0.5 Mg Tablet	60.00	30	Jo Do	412344	Bap	2/4	2.00 LME	Medicaid	FL
02/08/2022	09/28/2021	02/09/2022	1	Clonazepam 0.5 Mg Tablet	60.00	30	Jo Do	412344	Bap	1/4	2.00 LME	Medicaid	FL

https://florida.pmpaware.net/login

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Prescription Drug Monitoring Program (PDMP)

Red flags in the PDMP report:

- Multiple prescribers
- Multiple pharmacies
- Pharmacies far apart from each other
- Pharmacies far from patient and/or prescriber addresses
- Cash payments
- Drug cocktails: benzodiazepines, opioids, stimulants

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Prescription Drug Monitoring Program (PDMP)

Potential challenges with using the PDMP report may include:

- Misspelled patient names
- Wrong patient date of birth
- Wrong patient address
- Wrong date prescribed entered
- Wrong prescriber

Contact prescriber if something does not look correct

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Prescription Drug Monitoring Program (PDMP)

- PDMP data is confidential and considered protected health information
- PDMP may only be accessed for the purpose of reviewing information related to a patient of the prescriber or dispenser
- Law enforcement agencies do not have direct access to the PDMP but may request information from the PDMP for an active investigation to the Department of Health

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Knowledge Check

You must check PDMP before dispensing pregabalin for a 16-year-old patient in Florida.

a. True

b. False

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Take Home Points

- E-FORCSE™ is Florida's PDMP
- In most cases, checking the PDMP is a required step when verifying a controlled substance prescription
- Certain circumstances may not require the pharmacist to check the PDMP
- The PDMP provides very valuable information that can guide the pharmacist decision whether to dispense or not a prescription
- If the system is malfunctioning, you may document reason and dispense a maximum of a 3 days supply

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Patient Counseling

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Key Counseling Points

- Treatment Goals
- Administration
- Adverse Effects
- Interactions
- Storage and Disposal

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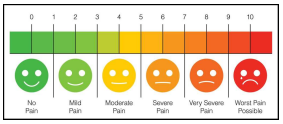
Treatment Goals

- For acute pain you may achieve a goal of no pain (0 points)
- Chronic pain patients need realistic treatment goals
- Multimodal pain management beyond opioids



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Administration

- Take as prescribed
- Follow directions on prescription label
- Do not alter original formulation
- Avoid alcohol consumption
- Take with or without regards to meals
- Do not drive or operate machinery

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Sharing is (Not Always) Caring

- Pill sharing among friends and family is a widespread practice
- Controlled substance sharing can lead to misuse, abuse, and addiction
- Potential for unknown drug interactions
- According to the Centers for Disease Control and Prevention (CDC), the number one source of abused prescription opioids is pills from friends and family

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Adverse Effects

Constipation	Itching	Drowsiness
Dry mouth	Nausea	Respiratory depression

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Management of Constipation

- Increasing dietary fiber, fluid intake, and physical exercise are the backbone to prevention therapy
- Bowel regimen may be necessary, especially if patients are receiving opioids around the clock
- All types of laxatives can be used as initial therapy except for the bulk-forming laxatives like psyllium
- The most common regimen is a stimulant (senna/bisacodyl) with or without a stool softener (docusate), or daily administration of an osmotic laxative (polyethylene glycol)

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Management of Itching

- Itching is common among patients taking opioids due to histamine release from mast cells
- Antihistamines are commonly used as first-line agents
- Patients may report it as an allergic reaction
- True opioid allergic reactions are very rare

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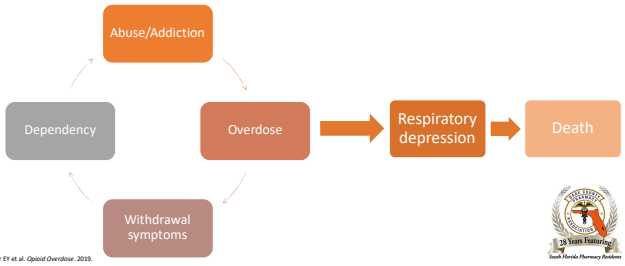
Serious Risks



Schiller EY et al. *Opioid Overdose*. 2019.

77

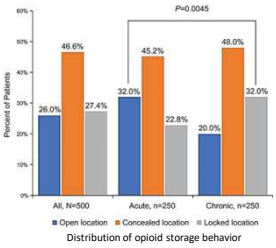
Interactions

Drug-drug	Drug-food	Drug-disease
Vitamins, minerals, and herbals	Inform healthcare providers	Alcohol intake

78

Storage

- Cool and dry place
- Secure location to prevent access by children/unauthorized people/pets
- Never share medication
- Only take it for as long as directed by prescriber
- Research has shown that nearly 79% of patients have unused opioid medication stored at home



Distribution of opioid storage behavior

Safe Opioid Storage and Disposal: A Survey of Patient Beliefs and Practices, 2020

79

Disposal

Goal: Get unused medications out of patient's homes

- DEA take back events
  1-2 days every year
- Authorized disposal sites
  Secure disposal kiosks in pharmacies or hospitals

Prescription safety, Centers for Disease Control and Prevention, 2021

80

Disposal

https://apps2.deadiversion.usdoj.gov/pubdispsearch/spring/main?execution=e1s1

Prescription safety, Centers for Disease Control and Prevention, 2021

81

Disposal

Remove the Risk

- FDA program
- Objective: Raise awareness of the dangers of keeping unused opioid pain medications at home and provide information on safe disposal

https://www.fda.gov/drugs/safe-disposal-medicines/safe-opioid-disposal-remove-risk-outreach-toolkit

Remove the RISK

82

Disposal

Remove the RISK

Remove the Risk Toolkit

- Spread the Word
- Social Media Graphics
- Video PSAs
- Social Media Posts
- Radio PSAs
- Fact Sheets
- Print PSAs
- Drop-in Content
- Posters & Postcards
- Website Badges

https://www.fda.gov/drugs/safe-disposal-medicines/safe-opioid-disposal-remove-risk-outreach-toolkit

83

No Disposal Sites, No Problem

- Read the label to look for special instructions on safe disposal of medication
- If no special instructions found:
  1. Mix your medicine with an inedible substance like dirt, cat litter, or used coffee grounds
  2. Put the mixture in a container, such as a sealed plastic bag
  3. Throw the container in your household trash
  4. Scratch out all the personal information on the prescription label of your empty medication bottle to make it unreadable
  5. Dispose or recycle the empty medication bottle

84

No Disposal Sites, No Problem

- Used patches
  - Dispose immediately upon removal
  - Do not cut the patch
  - Fold the adhesive side of the patch to itself
  - Flush down the toilet
- Unused patches
  - Remove patches from their pouches
  - Remove the protective liners
  - Do not cut the patch
  - Fold the adhesive side of the patch to itself
  - Flush down the toilet

85

Patient Counseling Key Points

- Upon receipt of a new or refill prescription, the pharmacist shall ensure that a verbal and printed offer to counsel is made to the patient or the patient's agent when present
- Patient or patient's agent may refuse counseling
- Counseling may include
  - Intended use of the drug
  - Directions of use
  - Length of therapy
  - Common side effects/additive side effects
  - Common drug interactions
  - Importance of taking medication as prescribed
  - Taking the minimum amount needed for pain relief

86

Knowledge Check

A patient's representative comes to your pharmacy to pick up a refill for zolpidem. Which one of the following statements is appropriate regarding patient counseling?

a. There is no need to offer counseling since it is not a new prescription
b. There is no need to offer counseling since the person picking up the prescription is not the patient
c. It is mandated by law that the pharmacist must counsel the patient's representative even if he/she refuses
d. A verbal and printed offer has to be made to the patient's representative

87

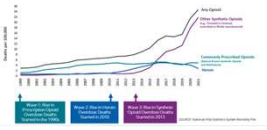
Opioid Use and Misuse

88

Overdose

- Nearly 645,000 people have died from overdoses involving opioids from 1999-2021
- Opioids were involved in more than 80,000 overdose deaths in 2021
- 400,000 opioid related deaths (1999-2017)
  - 1990: ↑ Prescribing opioids
  - 2010: ↑ Heroin overdose deaths
  - 2013: ↑ Synthetic opioid overdose deaths

Three Waves of Opioid Overdose Deaths



45 PEOPLE ..died each day from a **prescription opioid** overdose in 2021.

Opioid Overdose. Centers for Disease Control and Prevention. 2019.

89

Required By Florida Law

Controlled Substance House Bill 451

- The Florida Department of Health requires all health care providers to include non-opioid alternatives
  - Exception: Provision of emergency services of care or before providing anesthesia
- Health care practitioners must:
  - Inform the patient of available non-opioid alternatives
  - Discuss the advantages and disadvantages of non-opioid alternatives
  - Provide the patient with educational pamphlet
  - Document the non-opioid alternatives considered in the patient's record

House Bill No. 451: Chapter 2019-123.

90

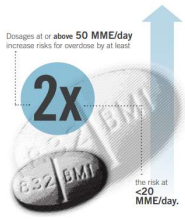
Risk Factors for Overdose

Dependency for chronic pain	Increasing doses for pain management	Doses > 50 MME/day
Concomitant severe medical or psychiatric conditions	Alcohol or other sedatives combination	Male gender
Younger age	Household members taking opioids	IV drug use history

Schiller EY et al. *Opioid Overdose*. 2019.

91

Milligrams of Morphine Equivalents (MME)



- Doses ≥ 50 MME/day increase overdose risk
- In a national survey of patients:
  - An average of 98 MME/day were prescribed for patients who died of opioid overdose
  - An average of 48 MME/day were prescribed to other patients
- Calculating MME/day helps identify those who may:
  - Benefit from closer monitoring
  - Reduction or tapering of opioids
  - Prescribing of naloxone

https://www.cdc.gov/drugoverdose/prescribing/guideline.html

92

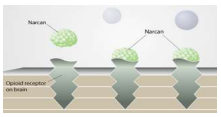
Milligrams of Morphine Equivalents (MME)

- Use caution when dispensing opioids at any dosage
- Use extra precautions when increasing to ≥50 MME per day such as:
  - Monitor and assess pain and function more frequently
  - Discuss reducing dose or tapering and discontinuing opioids if benefits do not outweigh harms
  - Consider offering naloxone
- Avoid or justify increasing dosage to ≥90 MME/day

93

Naloxone

- Mechanism
  - Opioid antagonist
- Administration
  - Intravenous, intramuscular, subcutaneous, & intranasal
- Onset of action
  - IV: 2 minutes
  - IM, SC: 2 to 5 minutes
  - Intranasal: 8 to 13 minutes
- Duration of action
  - 30 to 120 minutes depending on route
  - IV has a shorter duration of action than IM
    - Note: repeated doses are usually needed
- Dosing
  - Initial: 0.4 to 2 mg; may need to repeat doses every 2 to 3 minutes
- Adverse reactions:
  - Flushing, labile blood pressure, tachycardia, diaphoresis



Narcan Nasal Spray [prescribing information]. *Emergent Devices*. 2020.
Naloxone HCL Inj [prescribing information]. *AuroMedics Pharma*. 2019.

94

Who is Prescribed Naloxone?

- Title XXXII, Ch. 456.44 of Florida Pharmacy Law:
  - For the treatment of pain related to a traumatic injury
    - ISS of ≥9, a prescriber who prescribes a schedule II controlled substance **must concurrently prescribe an emergency opioid antagonist**, as defined in s. 381.887
- High risk populations:

History of substance abuse	Opioid doses > 50 MME/day	Benzodiazepine use	Sleep apnea
Pregnancy	Renal/hepatic disease	> 65 years old	Mental health comorbidities

Dreiling J. The Validation of Controlled Drug Prescriptions in Florida. 2020.

95

Who is Prescribed Naloxone?

2019 Florida statutes, Title XXIX, chapter 381.887:

"An authorized health care practitioner may prescribe and dispense an emergency opioid antagonist to a patient or caregiver for use in accordance with this section, and **pharmacists may dispense an emergency opioid antagonist pursuant to such a prescription or pursuant to a non-patient-specific standing order for an auto-injection delivery system or intranasal application delivery system**, which must be appropriately labeled with instructions for use"

Dreiling J. The Validation of Controlled Drug Prescriptions in Florida. 2020.

96

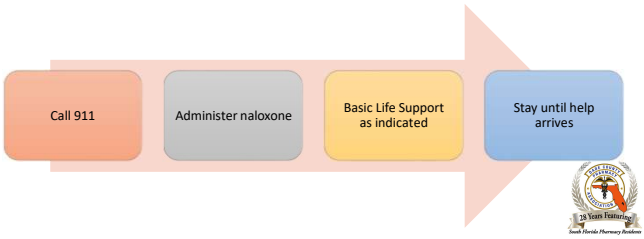
Recognizing an Overdose

Intoxication	Overdose
• Constricted pupils • Muscles are flaccid • Incoherence • Slurred speech • Disoriented • Little response to outside stimulus	• Pinpoint pupils • Loss of consciousness • Skin/nail/lip color changes • Awake but unable to speak • Unresponsive

Schiller EY et al. *Opioid Overdose*. 2019.

97

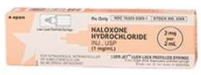
Responding to an Overdose



98

Dosage Forms

Naloxone Nasal Spray	Naloxone for Injection
• 4 mg/0.1 mL • Price: $50.00 • No prescription required • Available to the public	• Various doses available • Can be given as injection or intranasal with an atomizer



Narcan Nasal Spray [prescribing information]. *Emergent Devices*. 2020.
Naloxone HCL Inj [prescribing information]. *AuroMedics Pharma*. 2019.

99

Instructions for Use

Key Counseling Points:

- Do not prime
- Each box brings 2 devices
- Agitated and aggressive
- Administering naloxone will not hurt the patient if they do not have an overdose
- If the patient is overdosed not receiving naloxone could hurt them

Narcan Nasal Spray [prescribing information]. *Emergent Devices*. 2020.

100

Treatment Resources

www.myflfamilies.com/service-programs/samh

Substance Abuse and Mental Health (SAMH). Florida Department of Children and Families.

101

Treatment Resources

www.myflfamilies.com/service-programs/samh

Substance Abuse and Mental Health (SAMH). Florida Department of Children and Families.

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Treatment Resources

Find Local Services By County

If you or someone you know is in need of substance abuse and/or mental health services, our local managing entities can help you locate available programs. Please choose your county from the drop-down list below for the managing entity contact in your area.

County: Dade ▾ View local provider

Substance Abuse & Mental Health

Your Local Provider of Services

South Florida Behavioral Health Network

Telephone: 888-248-3111

Substance Abuse and Mental Health (SAMH). Florida Department of Children and Families.

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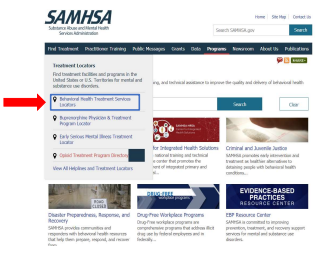
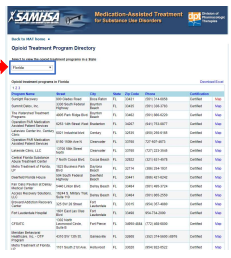
Treatment Resources



Substance Abuse and Mental Health (SAMH). Florida Department of Children and Families.

104

Treatment Resources



Substance Abuse and Mental Health (SAMH). Florida Department of Children and Families.

105

Treatment Resources

"Confidentiality of Alcohol and Drug Abuse Patient Records, Title 42 Code of Federal Regulations (CFR) Part 2" - "42 CFR Part 2"

- Governs confidentiality of alcohol and drug treatment and prevention information
- Extra protections because of the potential for substance use disorder (SUD) information to be used against an individual
  - Loss of employment, housing, child custody
  - Discrimination (health professionals, insurers)
  - Criminal consequence

106

Treatment Resources

If a patient receives treatment through an Opioid Treatment Program that information is **not** reported to state PDMP

- Protected by 42 CFR Part 2
- Methadone programs only "administer" and "dispense" methadone
- No medication is "prescribed"
- No prescription = no report to the state board of pharmacy
- Methadone clinics report daily to the State Opioid Treatment Authority (SOTA) in each state
- Patients may be aware of this, and still seek prescriptions of opioids for either personal use or to divert
- Exception: Methadone prescribed for pain will show up on the PDMP

107

Knowledge Check

You can get naloxone over the counter.

a. True
b. False

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Take Home Points

- Provide optimal patient education on the administration, adverse effects, drug interactions, and the appropriate storage and disposal during initial counseling with a new patient or new opioid agent
- Consult PDMP for each new prescription dispensed
- Dispense naloxone to any patient (caregiver) who could possibly be at a potential high risk for misuse or abuse
- Provide available treatment resources for patients with suspected dependence

109

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Thank you

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Slide 1

Updates In Oncology

Katherine Fernandez, Pharm.D.; Ryan Falcon, Pharm.D.
Baptist Hospital of Miami
Miami, Florida
January 20th, 2024

28 Years Featuring
South Florida Pharmacy Residents

Slide 2

Objectives

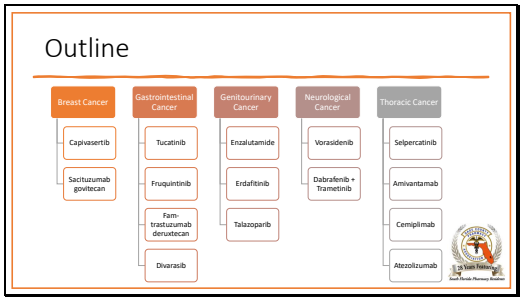
1. Identify newly approved oncolytic agents
2. Explain the clinical trials leading to approval of oncolytic agents
3. Evaluate clinical pearls and place in therapy for novel oncolytics
4. Define BiTE therapy
5. Analyze the potential place in therapy for BiTE therapy
6. Examine trials utilizing BiTE therapy

Slide 3

Abbreviations

- PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
- AKT1: AKT serine/threonine kinase 1
- PTEN: Phosphatase and tensin homolog
- LHRH: Luteinizing hormone-releasing hormone
- HR: Hormone receptor
- HER 2: Human epidermal growth factor receptor 2
- MAPK: Mitogen-activated protein kinase
- VEGFR: Vascular endothelial growth factor
- KRAS: Kirsten rat sarcoma virus
- FGFR: Pan fibroblast growth factor receptor
- PARP: Poly (ADP-ribose) polymerase
- IDH: Isocitrate dehydrogenase
- RET: Rearranged during transfection
- EGFR: Epidermal growth factor receptor
- MET: Mesenchymal-epithelial transition
- PD-1: Programmed death-1

Slide 4



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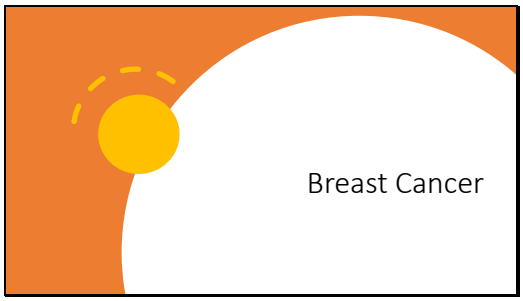

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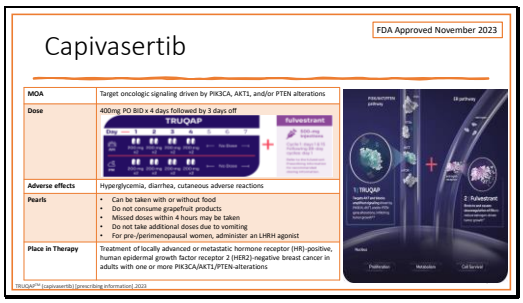


Slide 7

CAPItello-291

Outcomes	Methods	Results	Conclusions
Primary: • Progression-free survival assessed in both the overall population and among patients with AKT pathway altered tumors	Phase 3, randomized, double-blind (N=708) • 1:1 assignment of either capivasertib plus fulvestrant (n=355) or placebo plus fulvestrant (n=353)	Progression-free survival in overall populations: • 7.2 months in the capivasertib-fulvestrant group versus 3.6 months in the placebo-fulvestrant group Progression-free survival in AKT pathway altered group: • 7.3 months in the capivasertib-fulvestrant group, versus 3.1 months in the placebo-fulvestrant group	Capivasertib-fulvestrant therapy resulted in significantly longer progression-free survival than treatment with fulvestrant alone

Turner NC, et al. N Engl J Med. 2023; 1;388(22):2058-2070

Slide 8

Sacituzumab govitecan

MOA	• Antibody drug conjugate that consists of Trop-2 coupled to SN-38 via a cleavable link • Trop-2 is highly expressed in many epithelial cancer cell surfaces and is associated with cancer cell growth • Sacituzumab binds to Trop-2 and is internalized; SN-38 is released intracellularly leading to DNA damage, apoptosis and cell death	
Dose	10mg/kg on days 1 and 8 of a 21 day treatment cycle	
Adverse effects	Nausea, hypersensitivity/infusion reactions, GI toxicity	
Pearls	Black Box Warning: • Neutropenia • Diarrhea	
Place in Therapy	**New Indication:** • HR+/HER2- metastatic breast cancer in adults who have previously received endocrine therapy and at least two additional treatments for metastatic disease	Current Indications: • Metastatic breast cancer • Metastatic urothelial cancer

TRODELVY [package insert]. 2023.

Slide 9

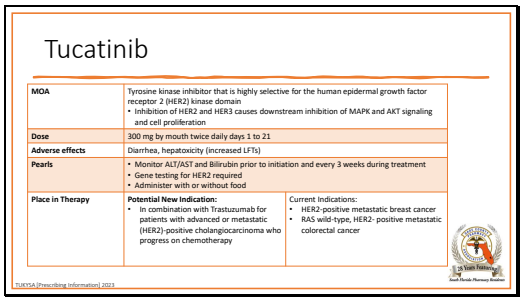
TROPiCS-02

Outcomes	Methods	Results	Conclusions
Primary: • Progression free survival Secondary: • Overall survival • Objective response rate	Randomized, open label, phase 3, 91 centers across North America (N=543) • 1:1 assignment of sacituzumab govitecan (n=272) or chemotherapy (n=271)	Progression free survival: • sacituzumab govitecan 5.5 months vs 4.0 months with chemotherapy Overall survival: • Overall survival was significantly improved with sacituzumab govitecan 14-4 months vs chemotherapy 11-2 months Objective response rate • sacituzumab govitecan 57 patients (21%) vs 38 (14%) with chemotherapy	Sacituzumab govitecan demonstrated statistically significant and clinically meaningful benefit over chemotherapy

Rugo HS, et al. Lancet. 2023; 21;402(10411):1423-1433

Slide 10

Slide 11



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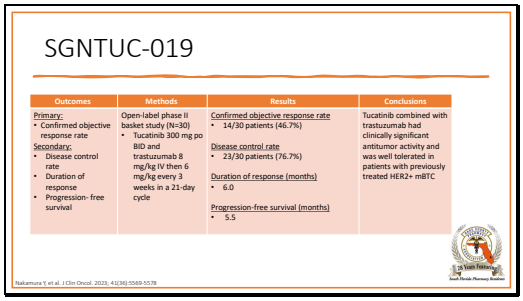

Slide 13

Fruquintinib

FDA Approved November 2023

MOA	• VEGFR 1, 2,3 inhibitor
	  • VEGFR is a key regulator of angiogenesis associated with tumor growth and metastasis
	  • Inhibition leads to decreased cell proliferation, tubular formation and tumor growth

Dose	5 mg once daily on days 1 to 21 of each 28 day cycle, continue until progression or unacceptable toxicity
Adverse effects	Dermatologic toxicity, GI perforation, hemorrhage, hypertension, infection, wound healing complications, arterial thromboembolism
Pearls	• Do not initiate unless blood pressure is adequately controlled • Withhold for ≥ 2 weeks prior to major surgery and do not resume until adequate wound healing has occurred
Place in Therapy	Patients with metastatic colorectal cancer who progress on multiple agents including chemotherapy, vascular endothelial growth factor inhibitors, and epidermal growth factor receptor inhibitors

Fruzaqla. Prescribing Information 2023.

Slide 14

FRESCO-2

Outcomes	Methods	Results	Conclusions
Primary: • Overall survival Secondary: • Progression free survival	Randomized, double-blind, phase 3 (N=691) • 2:1 fruquintinib (n=461) or matched placebo (n=230) orally once daily on days 1-21 in 28-day cycles, plus best supportive care	Overall survival • 7·4 months in the fruquintinib group versus 4·8 months in the placebo group Progression free survival • 3.7 months in the fruquintinib group vs 1.8 months in the placebo group	Fruquintinib treatment resulted in a significant and clinically meaningful benefit in overall survival compared with placebo in patients with refractory metastatic colorectal cancer.

Dasari A et al. Lancet. 2023; 1;402(10395):41-53

Slide 15

Knowledge Check

• True or False: Tucatinib is an anti-HER TKA inhibitor being studied for patients with (HER2)-positive cholangiocarcinoma.

Slide 16

Fam-trastuzumab deruxtecan

MOA	HER-2 directed antibody-drug conjugate • Deruxtecan component is a cleavable linker and the topoisomerase inhibitor that is released when bound to HER2 cells and causes DNA damage and cell death	
Dose	6.4 mg/kg once every 3 weeks until disease progression or unacceptable toxicity	
Adverse effects	Neutropenia, thrombocytopenia, cardiotoxicity (left ventricular dysfunction), infusion reactions and pulmonary toxicity	
Pearls	• Black box warnings • Interstitial lung disease • Embryo-fetal toxicity • HER-2 gene testing required for use	
Place in Therapy	**New Indication:** • Gastric cancer HER-2 positive	Current Indications: • Breast cancer; HER-2 low & HER-2 positive • Colorectal cancer HER-2 expressing • Non-small cell lung cancer HER-2 mutation positive

ENHERTU. Prescribing Information 2022.

Slide 17

DESTINY-Gastric01

Outcomes	Methods	Results	Conclusions
Primary outcome: • Objective response Secondary outcome: • Overall survival • Response duration • Confirmed response	Open label, randomized, phase 2 trial with adult patient in Japan and South Korea (N=188) • Randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan (n=125) or physician's choice of chemotherapy (n=62)	Objective response: • 51% in the trastuzumab deruxtecan group vs 14% in the physician's choice group Overall survival • 12.5 months in the trastuzumab deruxtecan group vs 8.4 months in the physician's choice group Response duration • 11.3 months in trastuzumab deruxtecan group vs 3.9 months in physician's choice group Confirmed response • 86% in trastuzumab deruxtecan group vs 63% in physician's choice group	Therapy with trastuzumab deruxtecan led to significant improvements in response and overall survival, as compared with standard therapies

Shitara K, Bang YJ, Iwasa S, et al. *N Engl J Med*. 2020;382(25):2419-2430.

Slide 18

DESTINY-Gastric02

Outcomes	Methods	Results	Conclusions
Primary outcome: • Confirmed objective response rate	Single arm, phase 2 study in adults from 24 sites in USA and Europe (N=79) • Patients were given 6-4 mg/kg of trastuzumab deruxtecan IV every 3 weeks until disease progression, withdrawal by patient, physician decision, or death	Objective response rate • 5.9 months: • 30 of 79 patients (38%) including 3 complete responses (4%) and 27 partial responses (34%) • 10.2 months • 33 of 79 patients (42%) including 4 completes responses (5%) and 29 partial responses (37%)	These clinically meaningful results support the use of trastuzumab deruxtecan as second-line therapy in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer

Van Cutsem E et al. Lancet Oncol. 2023; 24(7):744-756.

Slide 19

Divarasib

MOA	KRAS G12C inhibitor with high selectivity and potency • Binds to cysteine residue and irreversibly locks protein into its inactive state, turning off its oncogenic signaling
Dose	50-400mg once daily in 21 day cycles
Adverse Effects	N/V, diarrhea, fatigue, decreased appetite and increased AST/ALT reported in >10% of study participants
Potential Place in Therapy	• Patients with previously treated G12C KRAS-mutant Non-small cell lung cancer, colorectal cancer, or other solid cancers Under Regulatory Review

The KRAS G12C mutation favors the active form of the KRAS mutant protein, supporting tumorigenesis.[1]

Sacher A, LoRusso P, Patel MR et al. N Engl J Med. 2023 Aug 24;389(8):710-721

Slide 20

Single-Agent Divarasib (GDC-6036) in Solid Tumors with a KRAS G12C Mutation

Outcomes	Methods	Results	Conclusions

Primary outcome:
• Safety of Divarasib
 	
Secondary outcomes:
• Preliminary anti-tumor activity
• Biomarkers of response and resistance
	Ongoing phase 1, open-label, multicenter, dose-escalation, and dose-expansion study (N=137)	Safety:
		• No dose-limiting toxic effects were reported at any investigated dose (50 mg, 100 mg, 200 mg, or 400 mg once daily)
		• Nausea: 74%
		• Diarrhea: 61%
		• Vomiting: 58%
		Colorectal cancer (n=55)
		• Response rate:
		  • Complete response: 1/55 (2%)
		  • Partial response: 19/55 (35%)
		  • Stable disease: 27/55 (49%)
		  • Disease progression: 6/55 (11%)
		• Median time to response: 2.2 months
		• Median duration of response: 7.1 months
		• Biomarkers of response:
		  • Reduction in KRAS G12C variant allele frequency was observed as early as day 15 of cycle 1
			Treatment with divarasib resulted in durable clinical responses across KRAS G12C–positive tumors, with mostly low-grade adverse events

Sacher A, LoRusso P, Patel MR et al. N Engl J Med. 2023 Aug 24;389(8):710-721

Slide 21

Knowledge Check

• True or False Fruquintinib is a reasonable treatment option for treatment-refractory breast cancer

Slide 22

Genitourinary Cancer

Slide 23

Enzalutamide

MOA	Pure androgen receptor signaling inhibitor that inhibits androgen receptor nuclear translocation, DNA binding, and coactivator mobilization, leading to cellular apoptosis and decreased prostate tumor volume	
Dose	160 mg once daily until disease progression or unacceptable toxicity	
Adverse effects	Hypersensitivity reactions, ischemic heart disease, posterior reversable encephalopathy, seizures, falls & bone fractures	
Pearls	• Monitor prostate specific antigen levels (PSA) • Patients with partners who could become pregnant should use contraception during treatment and for 3 months after • No hepatic or renal adjustments necessary	
Place in Therapy	**New indication** • Initial treatment for prostate cancer with high-risk of biochemical recurrence in combination with androgen deprivation therapy	Current indications: • Castration resistant prostate cancer • Castration sensitive metastatic prostate cancer

XTANDI [package insert]. 2023.

Slide 24

EMBARK TRIAL

Outcomes	Methods	Results	Conclusions

Primary:
• Metastasis-free survival
 	
Secondary:
• Overall survival
• Safety
	Randomized, phase 3 trial (N=1068)
	• 1:1:1 ratio
	  • Enzalutamide daily plus leuprolide (n=355)
	  • Placebo plus leuprolide (n=358)
	  • Enzalutamide monotherapy (n=355)
		Metastasis-free survival
		• 87.3% in the combination group, 71.4% in the leuprolide-alone group, and 80.0% in the monotherapy group at 5 years
		
		Overall Survival
		• 5-year overall survival was 92.2% in the combination group, 87.2% in the leuprolide-alone group, and 89.5% in the monotherapy group
		
		Safety
		• The most common adverse events (≥10% of patients) in the combination group and the leuprolide-alone group were hot flashes and fatigue
		• The most common adverse events (≥30% of the patients) in the monotherapy group were gynecomastia, hot flashes and fatigue
			In patients with prostate cancer with high-risk biochemical recurrence, enzalutamide plus leuprolide was superior to leuprolide alone with respect to metastasis-free survival; enzalutamide monotherapy was also superior to leuprolide alone

Freedland SJ et al. N Engl J Med. 2023; 389(16):1453-1465.

Slide 25

Erdafitinib

MOA	Pan fibroblast growth factor receptor (FGFR) kinase inhibitor that binds to and inhibits FGFR1, FGFR2, FGFR3, and FGFR4 enzyme activity • FGFR inhibition results in decreased FGFR-related signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions
Dose	Initial: 8 mg once daily; after 14 to 21 days, if serum phosphate is <5.5 mg/dL, increase dose to 9 mg once daily based on tolerability, continue until disease progression or unacceptable toxicity
Adverse effects	Hyperphosphatemia, ocular toxicity, mouth sores, nail malformations
Pearls	• Assess serum phosphate levels 14 to 21 days after therapy initiation • Restrict phosphate intake to 600 to 800 mg daily • Swallow tablet whole, do not crush or chew • Can be taken with or without food
Place in Therapy	Patients with platinum-refractory metastatic urothelial carcinoma (UC) and an FGFR2 or FGFR3 alteration who progress on both chemotherapy and immunotherapy

BALVERSA® (Prescribing Information) 2023.

Slide 26

THOR

Outcomes	Methods	Results	Conclusions
Primary: • Overall survival Secondary • Progression free survival • Objective response • Response duration	Global, phase 3 trial (N=266) • 1:1 ratio to receive 21-day cycles of oral erdafitinib (n=136) (8 mg per day with increase in dose to 9mg on day 14) or the investigator's choice of chemotherapy (n=130)	Overall survival: • 12.1 months in the Erdafitinib group vs 7.8 months in the chemotherapy group at 15.9 month follow-up Progression free survival: • 5.6 months in the Erdafitinib group vs 2.7 months in the chemotherapy group Objective response: • Complete response: 9 patients (6.6%) • Partial response: 53 patients (39%) Response duration: • 4.9 months in the Erdafitinib group vs 5.6 months in the chemotherapy group	• Erdafitinib resulted in significantly longer overall survival than standard chemotherapy • Overall survival benefit of erdafitinib in patients with metastatic urothelial carcinoma with FGFR alterations supports molecular testing

Loriot Y et al. N Engl J Med. 2023; 23;389(21):1961-1971

Slide 27

Talazoparib

MOA	Poly (ADP-ribose) polymerase (PARP) enzyme inhibitor, including PARP1 and PARP2 • PARP enzymes are involved in DNA transcription, cell cycle regulation, and DNA repair that cause cell death due to accumulation of irreparable DNA damage when inhibited	
Dose	0.5 mg once daily (with enzalutamide) until disease progression or unacceptable toxicity	
Adverse effects	Hematologic toxicity (neutropenia, anemia, thrombocytopenia), secondary malignancy (MDS/AML), weakness, electrolyte abnormalities (hypokalemia, hypophosphatemia, hyponatremia, hypocalcemia)	
Pearls	• Renal dose adjustment required for CrCl <60 mL/min • Can be administered with or without food • Swallow capsules whole, do not crush, chew, or open	
Place in Therapy	**Potential new indication** • Metastatic castration-resistant prostate cancer in combination with enzalutamide with/without hrr gene mutation	Current indication • Metastatic or locally advanced BRCA-mutated, HER2 negative breast cancer • Metastatic castration-resistant prostate cancer with homologous recombination repair gene mutation

TALZENNA (package insert). 2023.

Slide 28

TALAPRO-2

Outcomes	Methods	Results	Conclusions
Primary: Radiographic progression free survival Secondary: • Overall survival • Objective Response rate	Randomized, double-blind, phase 3 (N=805) • Talazoparib + enzalutamide (n=402) • Placebo + enzalutamide (n=403)	Radiographic progression free survival • 37% lower risk in the talazoparib + enzalutamide group Overall survival • Pending, thus far 123/402 (31%) of patients in the talazoparib group and 58/132 (38%) in the placebo group have died Objective response rate • Complete response: 45/120 (38%) in talazoparib group vs 24/132 (18%) in placebo • Partial response: 29/120 (24%) in talazoparib vs 34/132 (26%) in placebo group	Results from the primary analysis of TALAPRO-2 trial support the consideration of talazoparib plus enzalutamide as a first-line treatment option in patients with mCRPC

Agarwal N et al. Lancet. 2023; 402(10398):291-303

Slide 29

Neurological Cancer

Slide 30

Vorasidenib

MOA	Dual inhibitor of the mutant IDH1 and IDH2 enzymes developed for penetration across the blood-brain barrier
Dose	40 mg oral daily in continuous 28 day cycle
Adverse effects	Increased LFTs, fatigue, headache, diarrhea, nausea, dizziness, seizures and constipation
Potential Place in Therapy	• Anticipated to be an important new option for patients with **IDH-mutant gliomas** who have not yet received radiation or chemotherapy Under Regulatory Review

Mellinghoff IK et al. N Engl J Med. 2023; 389(7):589-601

Slide 31

INDIGO

Outcomes	Methods	Results	Conclusions
Primary: Progression-free survival Secondary: • Time to next intervention	International, double-blind, randomized, placebo-controlled, phase 3 trial (N=331) • 1:1 ratio to receive vorasidenib (n=168) or placebo (n=163)	Progression-free survival • 27.7 months in the vorasidenib group vs 11.1 months in the placebo group Time to next intervention • No treatment intervention by 18 months: 85.6% in the vorasidenib group vs 47.4% in the placebo group • No treatment intervention by 24 months: 83.4% in the vorasidenib group vs 27.0% in the placebo group	This trial showed the single-agent activity of vorasidenib in patients with previously untreated WHO grade 2 glioma, additional trials will be necessary to define the role of vorasidenib in patient who have received cancer therapy previously

Mellinghoff IK et al. N Engl J Med. 2023; 389(7):589-601

Slide 32

Dabrafenib Plus Trametinib

	Dabrafenib	Trametinib
MOA	Selectively inhibits some mutated forms of the protein kinase B-raf (BRAF) • Inhibits tumor cell growth	Reversibly and selectively inhibits mitogen-activated extracellular kinase (MEK) 1 and 2 activation and kinase activity • MEK is a downstream effector of BRAF; BRAF V600 mutations result in activation of the BRAF pathway (including MEK1 and MEK2) • Decreased cellular proliferation, cell cycle arrest, and increased apoptosis
Dose	150 mg twice daily, approximately every 12 hours (in combination with trametinib) until disease progression or unacceptable toxicity	2 mg once daily (in combination with dabrafenib) until disease progression or unacceptable toxicity
Adverse effects	Cardiomyopathy, dermatologic toxicity, febrile reactions, hemorrhage, hyperglycemia, hemophagocytic lymphohistiocytosis, ocular toxicity, pulmonary toxicity, VTE	
Pearls	• BRAF mutation status must be confirmed for treatment	
Place in Therapy	**New indication:** • Low-grade glioma in pediatric patients	Current indications: • Melanoma with BRAF V600E or BRAF V600K mutation • Non-small cell lung cancer with BRAF V600E • Solid tumors with BRAF V600E • Thyroid cancer BRAF V600E

Mekinist (trametinib) [prescribing information]. 2023. Tafinlar (dabrafenib) [prescribing information]. 2023.

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Dabrafenib Plus Trametinib in Pediatric Glioma with BRAF V600 Mutations

Outcomes	Methods	Results	Conclusions
Primary: Overall response Secondary: • Duration of response • Progression-free survival	Phase 2 trial (N=110) • 2:1 ratio to receive a combination of oral dabrafenib plus trametinib once daily (n=73) or standard chemotherapy (carboplatin plus vincristine) (n=37)	Overall response • 34/73 (47%) of patient in the dabrafenib plus trametinib vs 4/37 (11%) in the chemotherapy group Duration of response • 20.3 months in the dabrafenib plus trametinib group vs 7.4 months in the chemotherapy group Progression-free survival • 87% in the dabrafenib plus trametinib group and 58% with chemotherapy at 6 months	• Superiority of dabrafenib plus trametinib as first systemic therapy for pediatric patients with low-grade glioma with BRAF V600 mutations • Findings show the value of early molecular testing for BRAF V600 mutation

Bouffet E et al. N Engl J Med. 2023; 389(12):1108-1120

Slide 34

Knowledge Check

- True or False Vorasidenib was studied in patients that have received radiation and chemotherapy

Slide 35

Thoracic Cancer

Slide 36

Selpercatinib

MOA	Highly selective anti-RET (REarranged during Transfection) kinase inhibitor • Inhibits wild-type RET, multiple mutated RET isoforms, VEGFR1 and VEGFR3 and FGFR 1, 2, and 3	
Dose	Patients ≥50 kg: Oral: 160 mg twice daily Patients <50 kg: Oral: 120 mg twice daily until disease progression or unacceptable toxicity	
Adverse effects	Hemorrhagic events, hypersensitivity reactions, hypertension, hypothyroidism, pulmonary toxicity, QT prolongation	
Pearls	• Test for presence of RET fusion gene • Withhold for 7 days prior to elective surgery and do not administer for 2 weeks following major surgery until wound healing has occurred	
Place in Therapy	**New indication:** • Non-small cell lung cancer RET fusion positive first-line therapy	Current indications: • Solid tumors, RET fusion positive • Thyroid cancer, RET fusion positive

Retevmo (selpercatinib). Prescribing Information 2023.

Slide 37

LIBRETTO-431

Outcomes	Methods	Results	Conclusions
Primary: Progression-free survival Secondary: • Overall survival • Percentage of patients with response • Duration of response	Randomized, phase 3 trial (N=212) • Patients were randomly assigned to receive either selpercatinib or pemetrexed along with the investigator's choice of platinum therapy	Progression-free survival • 24.8 months in the selpercatinib group vs 11.2 months with control treatment Overall survival • Interim analysis is showing 28.6% (50 deaths) based on the target number of 175 deaths Percentage of patients with an objective response • 84% in the selpercatinib group vs 65% in the control group Duration of response • 24.2 months with selpercatinib vs 11.5 months in the control group	Treatment with selpercatinib led to significantly longer progression-free survival than platinum-based chemotherapy with or without pembrolizumab

Zhou C et al. N Engl J Med. 2023; 16;389(20):1839-1850

Slide 38

Amivantamab

MOA	Bispecific antibody that targets both epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) • Blocks ligand binding and degrades EGFR and MET in exon 20 insertion models
Dose	**Patients <80 kg:** **Week 1:** IV: 1,050 mg split over days 1 and 2 (350 mg on day 1 and 700 mg on day 2). **Weeks 2 to 4**: 1,050 mg once weekly. **Subsequent infusions**: 1,050 mg once every 2 weeks **Patients ≥80 kg:** **Week 1**: 1,400 mg split over days 1 and 2 (350 mg on day 1 and 1,050 mg on day 2) **Weeks 2 to 4**: 1,400 mg once weekly. **Subsequent infusions**: 1,400 mg once every 2 weeks
Adverse effects	Dermatologic toxicity, ocular toxicity, pulmonary toxicity, infusion-related reactions
Pearls	Pre-medications recommended prior to infusion (antihistamine, antipyretic, and glucocorticoid)
Place in Therapy	Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations with chemotherapy

RYBREVANT® [Prescribing Information] 2021

Slide 39

CHRYSALIS

Outcomes	Methods	Results	Conclusions
Primary: • Incidence of dose-limiting toxicity • Overall response rate Secondary: • Duration of response • Progression-free survival • Clinical benefit rate	Phase I, open-label, dose-escalation, and dose-expansion study (N=158) • Amivantamab monotherapy after platinum-based chemotherapy, in patients who harbored EGFR Exon20ins mutations	Incidence of dose-limiting toxicity • No maximum tolerated dose was identified Overall response rate • 40% with 3 complete response and 29 partial response observed Duration of response • 11.1 months with 75% of responses observed at first disease assessment Progression-free survival • 8.3 months Clinical benefit rate • 74%	Amivantamab is the first bispecific antibody to demonstrate clinically meaningful efficacy in patients with EGFR Exon20ins NSCLC

Park K, et al. J Clin Oncol. 2021 Oct 20;39(30):3391-3402

Slide 40

PAPILLON

Outcomes	Methods	Results	Conclusions
Primary: Progression-free survival Secondary: • Objective response • Response duration	Phase 3, international, randomized trial (N=308) • 1:1 ratio patients with advanced NSCLC with EGFR exon 20 insertions amivantamab plus chemotherapy (n=153) or chemotherapy alone (n=155)	Progression-free survival • 11.4 months in the amivantamab-chemotherapy group vs 6.7 months in the chemotherapy group Objective response • Complete or partial; reported in 73% of patients in the amivantamab-chemotherapy group vs 47% with chemotherapy Response duration • 9.7 months in the amivantamab-chemotherapy group vs 4.4 months with chemotherapy	The use of amivantamab–chemotherapy resulted in superior efficacy as compared with chemotherapy alone as first-line treatment of patients with advanced NSCLC with EGFR exon 20 insertions

Zhou C et al. N Engl J Med. 2023; 389:2039-2051

Slide 41

Cemiplimab

MOA	Recombinant human IgG4 monoclonal antibody that inhibits programmed death-1 (PD-1) activity by binding to PD-1 and blocking the interactions with the ligands PD-L1 and PD-L2 restoring t-cell function	
Dose	**Single agent**: 350mg once every 3 weeks until disease progression or unacceptable toxicity **Combination treatment**: 350 mg once every 3 weeks (in combination with platinum-based chemotherapy) until disease progression or unacceptable toxicity, or for up to 108 weeks	
Adverse effects	Myocarditis, dermatologic toxicity (rash, DRESS, SJS) endocrinopathies (diabetes type 1, hyperthyroidism/hypothyroidism) colitis, neurologic toxicity, ocular disorders, pneumonitis	
Pearls	Patient selection for treatment based on PD-L1 expression (on ≥50% of tumor cells) for NSCLC	
Place in Therapy	**New indication:** • Metastatic non-small cell lung cancer; first-line single agent & first-line combination without an EGFR, ROS1, or ALK genetic mutation	Current indications: • Metastatic basal cell carcinoma • Metastatic or recurrent cervical cancer • Metastatic cutaneous squamous cell carcinoma

LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information 2023.

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EMPOWER-Lung 1

Outcomes	Methods	Results	Conclusions
Primary: Overall survival Secondary: • Objective response rate • Duration of response	Multicenter, open-label, global, phase 3 study (N=712) • Randomly assigned (1:1) to cemiplimab 350 mg (n=357) or platinum-doublet chemotherapy (n=355)	Overall survival • 21.9 months reached with cemiplimab vs 14.0 months with chemotherapy • At 35 months: 26.1 months in the cemiplimab group vs 13.3 months in the chemotherapy group Objective response rate • 39% in the cemiplimab group vs 20% in the chemotherapy group • At 35 months: 46% in the cemiplimab group vs 21% with chemotherapy Duration of response • 16.7 months for cemiplimab vs 6.0 months for chemotherapy • At 35 months: 23.3 months in the cemiplimab vs 5.9 months in the chemotherapy group	Clinically meaningful and statistically significant improvement in overall survival and progression-free survival with first-line cemiplimab monotherapy over platinum-doublet chemotherapy

Sezer A et al. Lancet. 2021; 397(10274):592-604

Slide 43

Atezolizumab

MOA	Humanized monoclonal antibody immune checkpoint inhibitor that binds PD-L1 to selectively prevent the interaction between PD-1 and B7.1 (also known as CD80) receptors, while still allowing interaction between PD-L2 and PD-1 • PD-L1 downregulates anti-tumor t-cell function and inhibition restores anti-tumor t-cell function
Dose	• 1,200 mg once every 3 weeks • Can also be used in combination with bevacizumab, paclitaxel, and carboplatin
Adverse effects	Cardiovascular toxicity, dermatologic toxicity, endocrinopathies, colitis, neurologic toxicities, myositis, ocular disorders, infusion reactions
Pearls	• PD-L1 expression status • Patients who could become pregnant should use effective contraception during therapy and for at least 5 months after the last atezolizumab dose
Place in Therapy	**Potential new indication** • Select patients with negative tumor PD-L1 and a poor performance status with non-small cell lung cancer Current indications • Alveolar soft part sarcoma • Hepatocellular carcinoma • Melanoma • Non-small cell lung cancer • Small cell lung cancer- first-line

TECENTRIQ Prescribing Information 2023

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IPSOS

Outcomes	Methods	Results	Conclusions
Primary: Overall survival Secondary: Overall survival rates at 6,12,18 and 24 months • Progression-free survival	Phase 3, open-label, randomized controlled study (N=453) • Randomized 2:1 by permuted-block randomization (block size of six) to receive 1200 mg of atezolizumab (n=302) or single-agent chemotherapy (n=151)	Overall survival • 10.3 months with Atezolizumab vs 9.2 months with chemotherapy Overall survival: **6 months**: 64% in the atezolizumab group vs 58% in the chemotherapy group **12 months**: 44% in atezolizumab group vs 39% in the chemotherapy group **18 months**: 31% in the atezolizumab group vs 24% in the chemotherapy group **24 months**: 24% in the atezolizumab group vs 12% in the chemotherapy group Progression-free survival • 4.2 months with atezolizumab vs 4.0 months with chemotherapy	First-line treatment with atezolizumab monotherapy was associated with improved overall survival compared with single-agent chemotherapy

Lee SM et al. Lancet. 2023;402(10400):451-463

Slide 45

Summary of Drugs

Newly Approved	Under Regulatory Review	Expanded Indications	Potentially Expanded Indications	New Efficacy Data
Capivasertib	Divarasib	Sacituzumab govitecan	Tucatinib	Erdafitinib
Fruquintinib	Vorasidenib	Fam-trastuzumab deruxtecan	Talazoparib	Amivantamab
		Enzalutamide	Atezolizumab	Selpercatinib
		Dabrafenib Plus Trametinib		
		Cemiplimab		

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BiTE Therapy

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Abbreviations

- B-ALL: B cell acute lymphoblastic leukemia
- BBW: black box warning
- CBC: complete blood count
- LFTs: liver function tests
- s/s: signs and symptoms
- TLS: tumor lysis syndrome
- FLAG: fludarabine + cytarabine + filgrastim
- HiDAC: high dose cytarabine
- HDMTX: high dose methotrexate
- DLBCL: diffuse large B cell lymphoma
- LDH: Lactate dehydrogenase
- CRP: C-reactive protein
- BBB: blood brain barrier
- Ca: Calcium
- K: potassium
- Na: sodium
- Phos: phosphorus
- Mg: magnesium
- SUBQ: subcutaneous
- ANC: absolute neutrophil count
- PLT: platelet count
- CrCl: creatinine clearance
- HLA-A: human leukocyte antigen A
- MHC: major histocompatibility complex
- scFV: single-chain variable fragment
- PI: proteosome inhibitor
- IMiD: immunomodulatory drug

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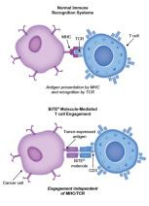
What is BiTE Therapy?

- BiTE: Bispecific T-cell engagers
- Mechanism: link endogenous T-cells to antigens expressed on tumors
  - Activates T-cells to eliminate targeted cell



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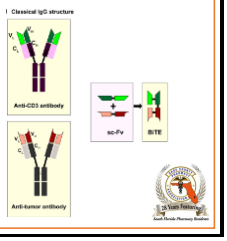
Construct

- Consists of 2 binding domains
  - Tumor expressed antigens: CD19, BCMA, DLL3
  - T-cells: CD3
- Binding domains
  - 2 single-chain variable fragment regions from antibodies



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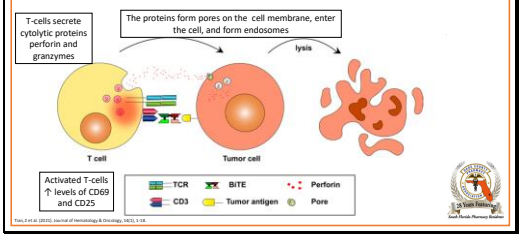
Mechanism of Action



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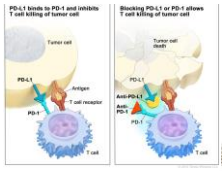
Mechanism of Escape

- Subset of patients have no response
  - Suppression of T-cells
    - Relationship with PD-1/PD-L1
  - Loss of target antigen



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Agents

- Blinatumomab
- Glofitamab
- Mosunetuzumab
- Talquetamab
- Tebentafusp

Slide 53

Blinatumomab (Blincyto®)

- Binding Domain: CD19 on B-cells
- Indication: B-ALL
- Adverse Reactions:
  - Hypertension
  - Hematologic abnormalities
  - Infection
  - Cytokine release syndrome (**BBW**)
  - Neurotoxicity (**BBW**)

Blinatumomab [prescribing information]. March 2018.

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Blinatumomab (Blincyto®)

Dosing

- Consolidation (four 6-week cycles):
  - ≥ 45 kg: 28 mcg daily
  - < 45 kg: 15 mcg/m^2/day (max: 28 mcg daily)
- Relapsed/Refractory:
  - ≥ 45 kg:
    - Cycle 1 (6 weeks): 9 mcg daily on D1-7, then 28 mcg on D8-28
    - Cycle 2-5 (6 weeks): 28 mcg daily on D1-28
    - Cycle 6-9 (12 weeks): 28 mcg daily on D1-28
  - < 45 kg:
    - Cycle 1 (6 weeks): 5 mcg/m^2/day on D1-7, then 28 mcg on D8-28
    - Cycle 2-5 (6 weeks): 15 mcg/m^2/day on D1-28
    - Cycle 6-9 (12 weeks): 15 mcg/m^2/day on D1-28

Administration

- 24 or 48 hr continuous infusion
- 7-day infusion
- Premedication: dexamethasone 16 mg 1 hr prior to first dose of each cycle

Monitoring

- CBC, LFTs
- s/s of CRS, neurotoxicity, infection, TLS

Blinatumomab [prescribing information]. March 2018.

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Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Design	Inclusion Criteria	Treatment	Results

• Prospective, randomized, phase 3 trial
• 101 centers in 21 countries
• Randomized in 2:1 ratio
• To receive:
  • Two cycles for induction
  • Three cycles for consolidation
  • Twelve months of maintenance therapy
Primary Outcome:
• Overall survival
	Inclusion:
	• Age ≥ 18
	• Ph-negative B-ALL (refractory/ relapse)
	• > 5% blasts in bone marrow
	• ECOG ≤ 2
		Blinatumomab (N=271):
		• 6-week cycles
		  • 9 mcg/day during week 1, then 28 mcg/day
		  • Two weeks off
		• Maintenance
		  • 4-week CI every 12 weeks
		Standard Chemotherapy Regimens (N=134):
		• FLAG ± anthracycline
		• HiDAC
		• HDMTX
		• Clofarabine
			• Overall Survival (in months):
			  • Blinatumomab: 7.7
			  • Chemotherapy: 4.0
			  • HR: 0.71; 95% CI, 0.55-0.93
			• Remission Rates (at 12 weeks):
			  • Blinatumomab: 34%
			  • Chemotherapy: 16%
			  • P<0.001
			• Event Free Survival (at 6 months):
			  • Blinatumomab: 31%
			  • Chemotherapy: 12%
			  • HR: 0.55; 95% CI, 0.43-0.71
			• Adverse Events (grade ≥ 3):
			  • Blinatumomab: 87%
			  • Chemotherapy: 92%

Kantarjian, H et al. (2017). *N Engl J Med*, *376*(9), 836-847.

Slide 56

Place in Therapy

Ph+ B-ALL	CR achieved	MRD + or -	Consolidation therapy with Blincyto®
Ph- B-ALL	CR achieved	MRD + or -	Consolidation therapy with Blincyto®
Relapsed/ Refractory	Blincyto®		

Blinatumomab [prescribing information]. March 2018.

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Knowledge Check

Which receptor does Blinatumomab target?

A. IL-19
B. CDK7
C. CD19
D. BRAF

Slide 58

Knowledge Check

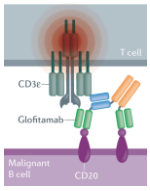
Which receptor does Blinatumomab target?

A. IL-19
B. CDK7
C. CD19
D. BRAF

Slide 59

Glofitamab (Columvi®)

- Binding Domain: Bivalent CD20 on B-cells
- Indication: DLBCL
- Adverse Reactions:
  - Rash
  - Hematologic abnormalities
  - Infection
  - Electrolyte abnormalities (↓ Ca, K, Na, Phos)
  - Cytokine release syndrome (**BBW**)



Glofitamab (prescribing information). June 2023.

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Glofitamab (Columvi®)

Dosing

- Relapsed/Refractory:
  - Cycle 1:
    - D1: Obinutuzumab
    - D8: 2.5 mg over 4 hrs
    - D15: 10 mg over 4 hrs
  - Cycle 2:
    - D1: 30 mg over 4 hrs
  - Cycles 3-12:
    - D1: 30 mg over 2 hrs

Administration

- Extend infusion time up to 8 hrs if CRS previously
- 0.2 micron filter needed
- Premedications: Dexamethasone 20 mg IV + Acetaminophen 500-1000 mg PO + Antihistamine

Monitoring

- CBC
- s/s of CRS, neurotoxicity, infection, TLS

Glofitamab (prescribing information). June 2023.

Slide 61

Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Design	Inclusion Criteria	Treatment	Results

• Phase 2 of an open-label phase 1-2 trial
• 155 patients enrolled
 	
Primary outcome:
• Complete response
	Inclusion:
	• Age ≥ 18
	• Relapsed/Refractory DLBCL
	• Received 2 previous therapies (containing 1 anti-CD20 drug and one anthracycline)
	• ECOG < 2
		• Pretreatment:
		  • Obinutuzumab 1 gm IV 7 days before first dose
		• Glofitamab (12 cycles):
		  • Cycle 1
		  • D8: 2.5 mg
		  • D15: 10 mg
		  • Cycle 2-12
		  • 30 mg on D1
			• Complete Response:
			  • Committee: 39%
			  • Investigator: 37%
			  • Historical control: 20%
			• Objective Response:
			  • Committee: 52%
			  • Investigator: 57%
			• Duration of Response (months):
			  • Complete: 19.8
			  • Objective:
			  • Committee: 18.4
			  • Investigator: 10.4
			• Adverse Events (grade ≥ 3):
			  • Occurred in 62% of patients
			  • Most common:
			  • CRS and neurologic events

Dickinson, M et al. (2022). N Eng J Med, 387(24), 2220-2231.

Slide 62

Place in Therapy

Relapsed/ Refractory → Failed at least two lines of systemic therapy * → Glofitamab or Epcoritamab

* Includes patients with disease progression after transplant or CAR-T

Glofitamab [prescribing information]. June 2023.

Slide 63

Mosunetuzumab (Lunsumio®)

- Binding Domain: CD20 on B-cells
- Indication: Follicular Lymphoma
- Adverse Reactions:
  - Rash
  - Hematologic abnormalities
  - Infection
  - Electrolyte abnormalities (↓ Mg, Phos, K)
  - Elevated LTFs
  - Hyperglycemia
  - Cytokine release syndrome (**BBW**)

Mosunetuzumab [prescribing information]. December 2022.

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Mosunetuzumab (Lunsumio®)

Dosing

- Relapsed/Refractory:
  - Cycle 1:
    - D1: 1 mg over 4 hrs
    - D8: 2 mg over 4 hrs
    - D15: 60 mg over 4 hrs
  - Cycle 2:
    - D1: 60 mg over 2 hrs
  - Cycles 3-8:
    - D1: 30 mg over 2 hrs

Administration

- Infuse over 2 hrs if cycle 1 infusions were tolerated
- Do not administer other medications through same line
- Premedications: Dexamethasone 20 mg IV + Acetaminophen 500-1000 mg PO + Antihistamine

Monitoring

- CBC
- s/s of CRS, neurotoxicity, infection, TLS

Mosunetuzumab [prescribing information]. December 2022.

Slide 65

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study

Design	Inclusion Criteria	Treatment	Results

• Single arm, multicenter phase 2 trial
• 49 centers in 7 countries
• 90 patients enrolled
 	
Primary outcome:
• Complete response
	Inclusion:
	• Age ≥ 18
	• Relapsed/Refractory follicular lymphoma
	• Received 2 previous therapies (containing 1 anti-CD20 drug and one alkylating agent)
	• ECOG < 2
		• Pretreatment:
		  • Dexamethasone 20 mg or equivalent
		• Mosunetuzumab:
		  • Cycle 1:
		  • D1: 1 mg
		  • D8: 2 mg
		  • D15: 60 mg
		  • Cycle 2:
		  • D1: 60 mg
		  • Cycle 3 and beyond:
		  • D1: 30 mg
		• Duration of treatment:
		  • 8 cycles for complete response
		  • 17 cycles for partial response
			• Complete Response:
			  • Committee: 60%
			  • Investigator: 60%
			  • Historical control: 14%
			• Objective Response:
			  • Committee: 80%
			  • Investigator: 77.8%
			• Duration of Response (12 months):
			  • Objective:
			  • Committee: 61.8%
			  • Investigator: 64.8%
			• Adverse Events:
			  • Most common:
			  • CRS, fatigue, and headache

Budde, L et al. (2022). The Lancet Oncology, 23(8), 1055–1065.

Slide 66

Place in Therapy

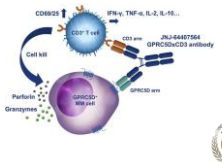
Relapsed/Refractory → Failed at least two lines of systemic therapy → Mosunetuzumab

Mosunetuzumab [prescribing information]. December 2022.

Slide 67

Talquetamab (Talvey®)

- Binding Domain: G protein-coupled receptor class C group 5 member D (GPRC5D)
- Indication: Multiple Myeloma
- Adverse Reactions:
  - Hypotension
  - Dermatologic disorders
  - Nail disease
  - Hematologic abnormalities
  - Infection
  - Electrolyte abnormalities (↓ Na, Phos, K)
  - Elevated LTFs
  - Weight loss
  - Cytokine release syndrome (**BBW**)
  - Neurotoxicity (**BBW**)



Talquetamab [prescribing information]. August 2023.

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Talquetamab (Talvey®)

Dosing

- Relapsed/Refractory:
  - Weekly:
    - D1: 0.01 mg/kg once
    - D4: 0.06 mg/kg once
    - D7: 0.4 mg/kg once
    - Weekly thereafter: 0.4 mg/kg weekly
  - Biweekly:
    - D1: 0.01 mg/kg once
    - D4: 0.06 mg/kg once
    - D7: 0.4 mg/kg once
    - D10: 0.8 mg/kg once
    - Biweekly thereafter: 0.8 mg/kg

Administration

- SUBQ only
- Administer into abdomen or thigh
- Use actual body weight
- Patients should remain hospitalized for 48 hrs post step-up dose
- Premedications: Dexamethasone 16 mg IV + Acetaminophen 500-1000 mg PO + Antihistamine
- REMS Program (TECVAYLI)

Monitoring

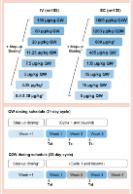
- CBC, LFTs, Bilirubin
- s/s of CRS, neurotoxicity, infection, TLS, skin toxicity

Talquetamab [prescribing information]. August 2023.

Slide 69

Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Design	Inclusion Criteria	Treatment	Results

• Phase 1 open-label multicenter study
• Composed of two phases:
  • Dose escalation
  • Dose expansion
• 232 patients enrolled
 	
Primary outcome:
• Frequency and type of toxicities
 	
Secondary outcomes:
• Response
• Pharmacokinetics
• Pharmacodynamics
• Immunogenicity
	Inclusion:
	• Age ≥ 18
	• Relapsed/refractory multiple myeloma
	• Utilized prior therapy containing a proteasome inhibitor and an immunomodulatory drug
	• ECOG < 2
	• ANC ≥ 1,000
	• PLT ≥ 50,000
	• CrCl ≥ 40
			• Frequency of toxicities (grade ≥ 3):
			  • 405 mcg SQ weekly: 87%
			  • 800 mcg SQ every 2 wk: 86%
			  • All IV doses: 90%
			• Most common adverse events:
			  • CRS
			  • Skin reactions
			  • Dysgeusia
			• Response:
			  • 405 mcg SQ weekly: 70%
			  • 800 mcg SQ every 2 wk: 64%
			  • Most SQ doses: 68%
			  • Most IV doses: 72%

Chari, A. (2022). N Engl J Med., 387(24), 2232-2244.

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Place in Therapy

Relapsed/ Refractory → After at least four prior therapies* → Talquetamab or Elranatamab or Teclistamab

- * Includes regimens with an anti-CD38 monoclonal antibody, PI, and an IMiD

Talquetamab [prescribing information]. August 2023.

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Knowledge Check

Talquetamab is indicated for which of the following indications?

A. Multiple Myeloma
B. Breast Cancer
C. Lymphoma
D. Pancreatic Cancer

Slide 72

Knowledge Check

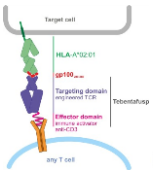
Talquetamab is indicated for which of the following indications?

A. Multiple Myeloma
B. Breast Cancer
C. Lymphoma
D. Pancreatic Cancer

Slide 73

Tebentafusp (Kimmtrak®)

- Binding Domain: gp100 peptide
- Indication: Uveal Melanoma
- Adverse Reactions:
  - Edema
  - Hypotension
  - Rash
  - Electrolyte abnormalities (↓ Na, Ca, Phos, K, Mg)
  - Hyperglycemia
  - GI upset
  - Hematologic abnormalities
  - Increased LFTs
  - Cytokine release syndrome (**BBW**)
  - Increased serum creatinine



Tebentafusp (prescribing information). January 2022.

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Tebentafusp (Kimmtrak®)

Dosing

- Unresectable or metastatic:
  - D1: 20 mcg
  - D8: 30 mcg
  - D15: 68 mcg
  - Day 22 and beyond: 68 mcg weekly
- Must be HLA-A*02:01-positive

Administration

- Over 15-20 minutes IV
- 0.2 micron filter
- Do not administer other medications through same line
- First 3 doses should be administered inpatient
- Premedications: none

Monitoring

- HLA-A*02:01 genotyping
- LFTs, bilirubin
- s/s of CRS, infection, TLS, skin toxicity

Tebentafusp (prescribing information). January 2022.

Slide 75

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Design	Inclusion Criteria	Treatment	Results

• Open-label phase 3 trial
• Randomized in 2:1 ratio
• 378 patients enrolled
 	
Primary outcome:
• Overall Survival
	Inclusion:
	• Age ≥ 18
	• Metastatic uveal melanoma
	• HLA-A*02:01-positive
	• At lease 1 measurable lesion
	• No previous systemic or liver-directed therapy
	• ECOG < 2
		• Tebentafusp (N=252)
		  • D1: 20 mcg
		  • D8: 30 mcg
		  • 68 mcg weekly thereafter
		• Investigator's choice (N=126)
		  • Pembrolizumab
		  • Ipilimumab
		  • Dacarbazine
			• Overall survival (at 1 year):
			  • Tebentafusp: 73%
			  • Investigator's choice: 59%
			• Duration of response (in months):
			  • Tebentafusp: 21.7
			  • Investigator's choice: 16.0
			• Common adverse events:
			  • CRS
			  • Skin related events

Nathan, P. et al. (2021). N Eng J Med, 385(13), 1196-1206.

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Place in Therapy

Metastatic or Unresectable Disease → HLA-A*02:01-positive → Tebentafusp

Tebentafusp (prescribing information). January 2022.

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CAR-T vs BiTE

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CAR-T vs BiTE

	Design	MHC Dependency	Mechanism of Cytotoxicity	Immune Escape
CAR-T	T-cells engineered genetically to target tumor cell antigen ex vivo	Independent	CAR-T cells themselves release perforin and granzyme B	Primarily due to loss of target antigen
BiTE	Soluble protein with two scFvs domains targeting CD3 on T-cells and an antigen on cancer cells	Independent	T-cells activated from BiTE release perforin and granzyme B	Due to loss of antigen and upregulation of immune checkpoints

Subklewe, M. (2022). Blood Advances, 5(2), 607-612.

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CAR-T vs BiTE

	Unique Toxicities	Efficacy	Availability
CAR-T	• Cytokine release syndrome • Immune effector cell associated neurotoxicity	Can engraft long term	• Requires ex vivo engineering of autologous T cells • Resource depleting • Time consuming • Cost: $$$$
BiTE	• Cytokine release syndrome • Immune effector cell associated neurotoxicity	Requires repeated IV infusions	• Readily available medications • Cost: $ - $$$

Subklewe, M. (2021). Blood Advances, 5(2), 607-612.

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Knowledge Check

Which of the following is FALSE in regard to BiTE therapy?

A. Mechanism of action is independent of MHC
B. Requires repeated infusions to maintain efficacy
C. Has similar toxicities to CAR-T therapy
D. Is more costly than CAR-T therapy

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Knowledge Check

Which of the following is FALSE in regard to BiTE therapy?

A. Mechanism of action is independent of MHC
B. Requires repeated infusions to maintain efficacy
C. Has similar toxicities to CAR-T therapy
D. Is more costly than CAR-T therapy

Slide 82

Cytokine Release Syndrome

Pathophysiology
Manifestations
Diagnosis
Management

Slide 83

Definition

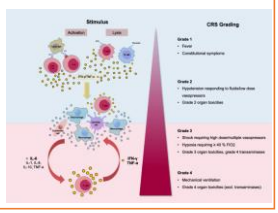
- Physiologic response resulting in the activation of immune effector cells
  - Endogenous of infused cells
  - Applies to any immune therapy
- Includes symptoms such as:
  - Fever at onset
  - Hypotension
  - End organ dysfunction

Lee, D. W et al. (2019). Biology of blood and marrow transplantation, 25(4), 625-638.

Slide 84

Pathophysiology

- Rapid release of cytokines due to immune therapy activating T cells
  - T cells release IFN-g
  - IFN-g activates macrophages
    - IL-6
    - TNF-alpha
    - IL-10
  - Cardiovascular, renal, neurological, and respiratory toxicity



Shimabukuro-Vornhagen, A et al. (2018). Journal for immunotherapy of cancer, 6(1), 1-14.

Slide 85

Manifestations

Physical	Laboratory
• Fever • Fatigue • Headache • Rash • Myalgia • Hypotension • Edema • Circulatory collapse • Vascular leakage • Multi organ system failure	• Leukocytosis • Hypophosphatemia • Hypokalemia • Hyponatremia • Elevated CRP • Elevated ferritin

Shimabukuro-Vornhagen, A et al. (2018). Journal for immunotherapy of cancer, 6(1), 1–14.

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Diagnosis

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.
Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache

- Should develop within hours to days after treatment
- Patient should be hospitalized for first 9 days of first cycle and for first 2 days of second cycle

Lee, D. W et al. (2019). Biology of blood and marrow transplantation, 25(4), 625–638.

Slide 87

Management

- Refer to drug specific package insert for management
- In general:
  - Interrupt BiTE therapy
  - Steroids (I.e. dexamethasone 8 mg Q8h)
  - Supportive care (IV fluids, respiratory support)
  - Tocilizumab 8 mg/kg once
    - If refractory to steroids
    - May repeat up to three doses
  - Anakinra
    - IV: 2 mg/kg/hr as CI for up to 72 hrs or 2-10 mg/kg/day in 2-4 doses
    - SQ: 2-10 mg/kg/day in 2-4 doses

Shimabukuro-Vornhagen, A et al. (2018). Journal for immunotherapy of cancer, 6(1), 1–14.

Slide 88

Immune Effector Cell-Associated Neurotoxicity Syndrome

Pathophysiology
Manifestations
Diagnosis
Management

Slide 89

Definition

- Pathologic process resulting in the activation of immune effector cells involving the central nervous system
  - Endogenous of infused cells
  - Applies to any immune therapy
- Includes symptoms such as:
  - Aphasia
  - Impaired cognition
  - Seizures
  - Cerebral edema

Lee, D. W et al. (2019). Biology of blood and marrow transplantation, 25(4), 625-638.

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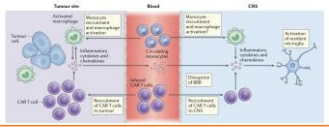
Pathophysiology

- Not fully understood
- Similar to CRS as cytokines are released once T cells are activated
  - Cytokines diffuse through the BBB
  - Activate microglial cells



Neel, J. H. (2022). The ASBMT/SHA CAR T-Cell Handbook, 141-145.

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Manifestations

Physical	Laboratory
• Confusion • Behavioral changes • Hallucinations • Headache • Language dysfunction • Seizures • Cerebral edema	• Elevated LDH • Thrombocytopenia • Elevated CRP • Elevated ferritin

Lee, D. W. et al. (2019). Biology of blood and marrow transplantation, 25(4), 625-638.

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Diagnosis

ICANS	ICE score[2]	7–9	3–6	0–2	0
	Depressed consciousness not attributable to other cause	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Arousable with vigorous tactile stimuli, unarousable, stupor, or coma
	Seizures	NA	NA	Any seizure with rapid clinical resolution or with intervention on EEG tracings	Prolonged (>5 min), non-resolving or life-threatening seizures
	Motor findings	NA	NA	NA	Significant focal motor weakness (eg, hemiparesis or paraparesis)
	Elevated ICP/ cerebral edema[3]	NA	NA	Focal edema on brain imaging	Diffuse edema on imaging, or decerebrate/decorticate posturing, CN VI palsy, or Cushing's triad

Lee, D. W. et al. (2019). Biology of blood and marrow transplantation, 25(4), 625-638.

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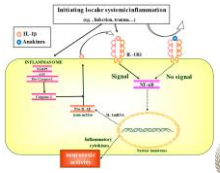
Management

- Refer to drug specific package insert for management
- In general:
  - Interrupt BiTE therapy
  - Steroids (I.e. dexamethasone 10-20 mg Q8h)
  - Seizure treatment: Levetiracetam
  - Anakinra (if refractory to steroids)
    - IV: 2 mg/kg/hr as CI for up to 72 hrs or 2-10 mg/kg/day in 2-4 doses
    - SQ: 2-10 mg/kg/day in 2-4 doses



Rees, J. H. (2022). The BRMT/EHA CAR-T Cell Handbook, 161-165.

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In Summary

- BiTE therapy has emerged as a strong option in the relapsed/refractory setting of multiple malignancies
- Pharmacist's role in ensuring safety is key:
  - Must monitor for signs and symptoms of unique toxicities
  - Ensure appropriate dosing and administration
  - Review for premedication utilization

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Slide 98

Updates In Oncology

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DADE COUNTY PHARMACY ASSOCIATION
28 Years Featuring
South Florida Pharmacy Residents

CAR-T Cell Therapy

Andrew S. Barnhart, Pharm.D.
PGY1 Resident at Baptist Hospital of Miami
Miami, FL
January 20th, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

Objectives

1. Describe the background of CAR T-cell therapy
2. Identify the FDA approved CAR T-Cell therapies
3. Recognize the potential complications of CAR T-cell therapy

2

Background

History of Chimeric Antigen Receptor (CAR)-T Cell Therapy
Mechanism of Action (MOA) – T Cells
CAR-T Cell: A Living Drug
Costimulatory Domain - 19 (CD19) Target
MOA – CAR-T Therapy
B-Cell Maturation Antigen (BCMA) Target

3

History of Chimeric Antigen Receptor (CAR)-T Cell Therapy

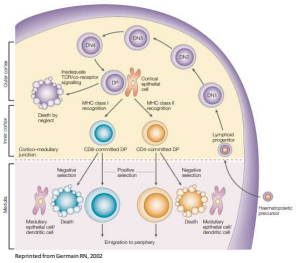
1960s	1970s	1990s	2000s	2017
• Animal studies showcased that immune cells could kill cancer cells	• First allogenic transplant	• Virus-specific T cells help decrease graft-vs-host disease and post transplant infections	• Creation of prostate cancer specific CAR-T cell therapy • Targeting leukemia cells by using CAR-T cell therapy specific to Costimulatory Domain - 19 (CD19)	• FDA approval of first CD19 CAR-T cell therapy for relapse or refractory acute lymphoblastic leukemia (ALL) in adolescent and young adults (AYA)

FDA: Food and Drug Administration
Memorial Sloan Kettering Cancer Center. www.mskcc.org. Updated 2023.

4

Mechanism of Action of T Cells

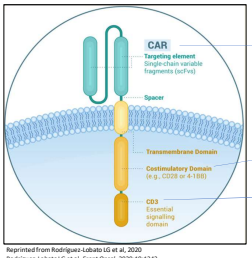
- T cell differentiation happens in the thymus
- Hematopoietic precursors → Lymphoid progenitor → Double negative (DN) thymocytes → double positive (DP) thymocyte
- DP with high affinity to major histocompatibility complex (MHC) class I molecules → CD8 T cells (cytotoxic)
- DP with high affinity to MHC class II molecules → CD4 T cells (helper)



Germain RN. *Nat Rev Immunol.* 2002; 2(5):309-322.
Reprinted from Germain RN, 2002

5

CAR-T Cell: A Living Drug



- Binds with either costimulatory domain 19 (CD19) or B-cell maturation antigen (BCMA)
- Promote CAR-T cell proliferation and survival
- First signal for T-cell activation

Reprinted from Rodriguez-Lobato LG et al. 2020
Rodriguez-Lobato LG et al. *Front Oncol.* 2020;10:1243.

6

Costimulatory Domain - 19 (CD19) Target

Highly expressed target antigen → Expressed by B-cell leukemias and lymphomas → Only in B-cell lineage

Subklewe M et al. *Transfus Med Hemother*. 2019;46(1):15-24.

7

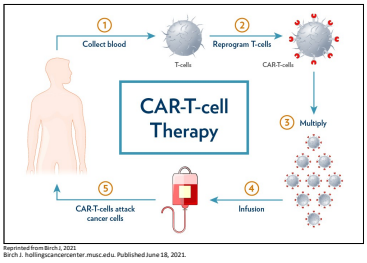
B-Cell Maturation Antigen (BCMA) Target

Expressed in plasma cells and late memory B cells → High expression with multiple myeloma cells → Not expressed in hemopoietic stem cells, naïve B-cells, non-hemopoietic tissues

Rodriguez-Lobato LG et al. *Front Oncol*. 2020;10:1243.

8

Mechanism of Action of CAR-T Cell Therapy



Reprinted from Birch J. 2021.
Birch J. hollingscancercenter.musc.edu. Published June 18, 2021.

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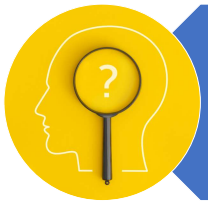
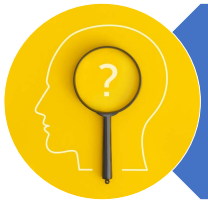
Question #1



CAR T-cell therapy utilizes chimeric antigen receptors (CARs) to help modify a patient's T cells to better attack their cancer cells. (True/False)

10

Question #1



CAR T-cell therapy utilizes chimeric antigen receptors (CARs) to help modify a patient's T cells to better attack their cancer cells. (True/False)

11

Place in Oncology

CAR-T Cell Therapies on the Market

Indications for Use

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CAR-T Cell Therapies on the Market

- 2017: • Tisagenleceucel (Kymriah®)
- 2018: • Axicabtagene Ciloleucel (Yescarta®)
- 2020: • Brexucabtagene Autoleucel (Tecartus®)
- 2021: • Lisocabtagene Maraleucel (Breyanzi®) • Idecabtogene Vicleucel (Abecma®)
- 2022: • Ciltacabtagene Autoleucel (Carvykti®)

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Indications for Use

- Pediatric Acute Lymphoblastic Leukemia (ALL)
- Large B Cell Lymphoma (LBCL)
- Follicular Lymphoma (FL)
- Mantle Cell Lymphoma (MCL)
- B-Cell ALL
- Multiple Myeloma

Carvykti [package insert]. Somerset, NJ: Janssen Biotech; Updated February 2023; Abecma [package insert]. Summit, NJ: Celgene Corporation; Updated October 2022; Yescarta [package insert]. Santa Monica, CA: Kite Pharma; Updated April 2022; Breyanzi [package insert]. Bothell, WA: Juno Therapeutics; Updated June 2023;Tecartus [package insert]. Santa Monica, CA: Kite Pharma; Updated August 2023; Kymriah [package insert]. Morris Plains, NJ: Novartis; Updated August 2023.

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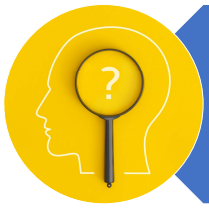
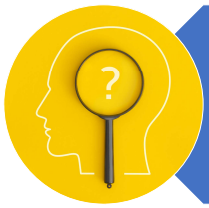
Question #2



CAR T-cell therapy can be utilized in any form of cancer. (True/False)

15

Question #2



CAR T-cell therapy can be utilized in any form of cancer. (True/False)

16

FDA Approved CAR-T Therapies - CD19

Tisagenlecleucel (Kymriah®)
Axicabtagene Ciloleucel (Yescarta®)
Brexucabtagene Autoleucel (Tecartus®)
Lisocabtagene Maraleucel (Breyanzi®)
CD19 CAR-T Cell Therapy Comparison

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Tisagenlecleucel (Kymriah®)

Characteristics	Tisa-cel
Indications	1. Refractory or relapsed AYA B-ALL 2. Adult refractory or relapsed LBCL 3. Adult refractory or relapsed FL
Dosing	Pediatric: • < 50 kg → 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg IV • > 50 kg → 0.1 to 2.5 x 10^8 CAR-positive viable T cells IV Adult: • 0.6 to 6.0 x 10^8 CAR-positive viable T cells

ELARA Trial

- 94 FL patients with ≥ 2 relapses
- Safety and efficacy of tisa-cel
- Overall response rate (ORR) 86.2% and complete response rate (CRR) 69.1%
- Cytokine release syndrome (CRS) 48.5%, neurologic events 37.1%, and immune effector cell-associated neurotoxicity syndrome (ICANS) 4.1%
- Tisa-cel is safe and effective in relapse or refractory FL

Kg: Kilograms, IV: Intravenous
Kymriah [package insert]. Morris Plains, NJ: Novartis; Updated August 2023;

18

Axicabtagene Ciloleucel (Yescarta®)

Characteristics	Axi-Cel
Indications	1. Adult refractory or relapsed LBCL 2. Adult refractory or relapsed FL
Dosing	2.0 x 10^6 CAR-positive viable T cells per kg • Max: 2.0 x 10^8 CAR-positive viable T cells

Zuma-7

- 359 LBCL patients with relapsed or refractory disease < 12 months prior to randomization
- Compared axi-cel to standard of care (SOC)
- 24-month event free survival (EFS) was 41% in axi-cel and 16% in SOC
- ≥ 3 grade ADEs was 91% in axi-cel and 83% in SOC
- Axi-cel provided better response than SOC with the expected higher toxicity of CAR-T therapy

ADE: Adverse drug event

Yescarta [package insert]. Santa Monica, CA: Kite Pharma; Updated April 2022; Locke FL et al. *N Engl J Med.* 2022;386(7):640-654.

19

Brexucabtagene Autoleucel (Tecartus®)

Zuma-2 Trial

- 74 MCL patients with failure on an Bruton's tyrosine kinase (BTK) inhibitor
- Safety and efficacy of brexu-cel
- Objective response 85% and complete response (CR) 59%
- Common ADEs were infection, CRS, and neurological events
- Brexu-cel resulted in a remission for many patients, but caused severe ADEs

Zuma-3 Trial

- 71 relapsed or refractory ALL, but 55 patients treated with brexu-cel
- CR 56% at 16.4 follow-up and median overall survival (OS) was 18.2 months
- Common ADEs were infection, CRS, and neurological events
- Brexu-cel provided high rates of complete remission with manageable ADEs

Characteristics	Brexu-Cel
Indications	1. Adult refractory or relapsed MCL 2. Adult refractory or relapsed B-ALL
Dosing	MCL: 2.0 x 10^6 CAR-positive viable T cells per kg • Max: 2.0 x 10^8 CAR-positive viable T cells B-ALL:1.0 x 10^6 CAR-positive viable T cells per kg • Max: 1.0 x 10^8 CAR-positive viable T cells

Yescarta [package insert]. Santa Monica, CA: Kite Pharma; Updated April 2022; Locke FL et al. *N Engl J Med.* 2022;386(7):640-654; Shah BD et al. *Lancet.* 2021;398(10299):491-502.

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Lisocabtagene Maraleucel (Breyanzi®)

Characteristics	Liso-Cel
Indications	1. Adult refractory or relapsed LBCL
Dosing	LBCL After One Line of Therapy: • 110 x 10^6 CAR-positive viable T cells LBCL After Two or More Lines of Therapy: • 50 x 10^6 CAR-positive viable T cells

Transform Trial

- 184 LBCL patients with relapsed or refractory status
- Compared liso-cel to standard of care (SOC) second line therapy
- EFS and PFS were increased in liso-cel compared to SOC, but both did not meet power
- Common ADEs were bone marrow suppression (BMS), HA, nausea, and CRS
- Liso-cel shows potential as a preferred second-line treatment for relapsed or refractory LBCL

HA: Headache

Breyanzi [package insert]. Bothell, WA: Juno Therapeutics; Updated June 2023; Abramson JS et al. *Blood.* 2023;141(14):1675-1684.

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CD19 CAR-T Cell Therapy Comparison

Characteristics	Tisagenlecleucel (tisa-cel)	Axicabtagene ciloleucel (axi-cel)	Brexucabtagene autoleucel (brexu-cel)	Lisocabtagene maraleucel (liso-cel)
Brand Name	Kymriah®	Yescarta®	Tecartus®	Breyanzi®
ADRs	**BBW:** CRS, ICANS, and REMS program **Common:** Fever, CRS, muscle pain, infection, BMS, GI upset, HA, encephalopathy and fatigue			
	Common: Hemorrhage and hypogammaglobulinemia	**Common:** Tachycardia and decreased phosphate	**Common:** Edema, hypotension, rash, hypoxia, and tremor	**None**
Premedications	Acetaminophen and H1-antihistamine			
Clinical Pearls	• Lymphodepleting regimen → Cyclophosphamide + Fludarabine • Not indicated for patients with CNS lymphoma except Tecartus®			

REMS: Risk Evaluation and Mitigation, GI: Gastrointestinal, CNS: Central nervous system
Yescarta [package insert]. Santa Monica, CA: Kite Pharma; Updated April 2022;Breyanzi [package insert]. Bothell, WA: Juno Therapeutics; Updated June 2023;Tecartus [package insert]. Santa Monica, CA: Kite Pharma; Updated August 2023; Kymriah [package insert]. Morris Plains, NJ: Novartis; Updated August 2023.

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FDA Approved CAR-T Therapies - BCMA

Idecabtogene Vicleucel (Abecma®)
Ciltacabtagene Autoleucel (Carvykti®)

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Idecabtagene Vicleucel (Abecma®)

Characteristics	Ide-Cel
Indication	Adult refractory or relapsed MM
Dosing	• 300 to 460 x 10^6 CAR-positive viable T cells

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

- 128 MM patients with ≥ 3 relapses
- Safety and efficacy of Ide-Cel
- Partial response 73% and CR 33%
- Common ADEs were BMS, CRS, and infections
- Cilta-cel resulted in a response for most patients, but grade 3/4 ADEs were very common

Abecma [package insert]. Summit, NJ: Celgene Corporation; Updated October 2022; Munshi NC et al. *N Engl J Med.* 2021;384(8):705-716.

24

Ciltacabtagene Autoleucel (Carvykti®)

Characteristics	Cilta-Cel
Indication	1. Adult refractory or relapsed MM
Dosing	• 0.5 to 1.0 x 10^6 CAR-positive viable T cells per kg • Max: 1.0 x 10^8 CAR-positive viable T cells

CARTITUDE-1 Trial

- 97 MM patients with ≥ 3 relapses
- Safety and efficacy of Cilta-cel
- 12-month progression free survival (PFS) 77% and OS 89%
- Common ADEs were BMS and CRS
- Cilta-cel resulted in a quick response and manageable ADEs

Carvykti [package insert]. Somerset, NJ: Janssen Biotech; Updated February 2023; Berdeja JG et al. *Lancet*. 2021;398(10297):314-324.

25

BCMA CAR-T Cell Therapy Comparison

Characteristics	Idecabtagene vicleucel (ide-cel)	Ciltacabtagene autoleucel (cilta-cel)
Brand Name	Abecma®	Carvykti®
ADRs	**BBW:** CRS, ICANS, REMS program, Hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and prolonged cytopenia with bleeding/infection **Common:** Fever, CRS, muscle pain, infection, BMS, GI upset, encephalopathy, hypogammaglobinemia and fatigue	
	None	**BBW:** Parkinsonism and Guillain-Barre Syndrome **Common:** Hypotension
Premedications	Acetaminophen and H1-antihistamine	
Clinical Pearls	• Lymphodepleting regimen → Cyclophosphamide + Fludarabine • Not indicated for patients with CNS lymphoma • Avoid prophylactic use of systemic corticosteroids	

Carvykti [package insert]. Somerset, NJ: Janssen Biotech; Updated February 2023; Abecma [package insert]. Summit, NJ: Celgene Corporation; Updated October 2022

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Place in Therapy

Acute Lymphoblastic Leukemia
Large B-Cell Lymphoma
Follicular Lymphoma
Mantle Cell Lymphoma
Multiple Myeloma

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Acute Lymphoblastic Leukemia

Indication	National Comprehensive Cancer Network (NCCN) Level of Recommendation	Product
< 26 years old and ≥ 2 relapses	No Level	Tisagenlecleucel (Kymriah®)
≥ 2 relapses	No Level	Brexucabtagene Autoleucel (Tecartus®)

National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia. Updated October 9, 2023.

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Large B-Cell Lymphoma

Indication	NCCN Level of Recommendation	Products
Relapsed disease < 12 months or primary refractory disease	Category 1	Axicabtagene Ciloleucel (Yescarta®)
		Lisocabtagene Maraleucel (Breyanzi®)
Relapsed disease > 12 months or refractory disease without intention for transplant	No Level	Lisocabtagene Maraleucel (Breyanzi®)
≥ 2 relapses	No Level	Axicabtagene Ciloleucel (Yescarta®)
		Lisocabtagene Maraleucel (Breyanzi®)
		Tisagenlecleucel (Kymriah®)

National Comprehensive Cancer Network. B-Cell Lymphoma. Updated October 10, 2023.

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Follicular Lymphoma

Indication	NCCN Level of Recommendation	Products
≥ 2 relapses	No Level	Axicabtagene Ciloleucel (Yescarta®)
		Tisagenlecleucel (Kymriah®)

National Comprehensive Cancer Network. B-Cell Lymphoma. Updated October 10, 2023.

30

Mantle Cell Lymphoma

Indication	NCCN Level of Recommendation	Products
≥ 2 relapses and failed chemotherapy and Bruton's tyrosine kinase (BTK) inhibitor	No Level	Brexucabtagene Autoleucel (Tecartus®)

National Comprehensive Cancer Network. B-Cell Lymphoma. Updated October 10, 2023.

31

Multiple Myeloma

Indication	NCCN Level of Recommendation	Products
≥ 3 relapses	No Level	Idecabtagene Vicleucel (Abecma®)
		Ciltacabtagene Autoleucel (Carvykti®)

National Comprehensive Cancer Network. Multiple Myeloma. Updated November 1, 2023.

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Opportunistic Infection Prophylaxis

Infection Prophylaxis Summary

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Infection Prophylaxis Summary

Infection	Prophylaxis Timeframe	Antimicrobials
Bacterial	During neutropenia and until ANC > 500	Levofloxacin
Viral	Lymphodepletion until 6-12 months post CAR-T therapy	Acyclovir, Valacyclovir
PCP	Lymphodepletion until 6-12 months post CAR-T therapy	Trimethoprim-Sulfamethoxazole, Atovaquone
Fungal	Not commonly used • Exceptions: Corticosteroid use, prior allogenic transplant, and/or history of invasive aspergillosis infection • If used, during neutropenia and until ANC > 500	Posaconazole, Micafungin

ANC: Absolute Neutrophil Count
Jain T et al. *Blood*. 2023;141(20):2460-2469; Stewart AG et al. *Ther Adv Infect Dis*. 2021;8:20499361211036773; National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections. Updated December 5, 2023.

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Cytokine Release Syndrome (CRS)

Definition
Pathophysiology
Presentation
Diagnosis
Grading
Management
Tocilizumab (Actemra)

35

Definition

American Society for Transplantation and Cellular Therapy (ASTCT)

- Reaction to immune therapy that leads to activation of immune cells. Symptoms must include fever, but can also include hypoxia, hypotension, and/or end organ dysfunction.

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

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Pathophysiology

T Cell activation increases inflammatory cytokines

- Cytokines – IL-6, IL-2, interferon-γ

Risk Factors (Severe CRS):

- Lymphodepletion with fludarabine
- Dose of CAR-T
- Concurrent infections
- High disease burden
- Early increase in cytokines

IL-6: Interleukin 6, IL-2: Interleukin 2
Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638; Neelapu SS et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62; Frey N et al. *Biol Blood Marrow Transplant.* 2019;25(4):e123-e127.

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Presentation

Symptoms

- Fatigue, chills, hypotension, hypoxia, tachycardia, headache

Onset

- Usually within 14 days of CAR-T or other immune effector cell-engaging therapy
- CRS can be considered past 14 days, but other sources must be ruled out

Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638; Neelapu SS et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

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Diagnosis

Labs

- Fever ≥ 100.4 °F
- Decreased oxygen saturation
- Increased C-reactive protein (CRP) and ferritin
  - Might correlate with IL-6 levels
- Increased overall cytokines in blood
- Increased HR + Decreased BP
- Disseminated intravascular coagulation → Increased PT, aPTT, and D-dimer
- Increased LFTs and total bilirubin

HR: Heart Rate, BP: Blood Pressure, PT: Prothrombin Time, aPTT: Activated Partial Thromboplastin Time, LFT: Liver Function Test
Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638; Neelapu SS et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

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Grading

Pieces:

- Fever ≥ 100.4 °F or ≥ 38 °C
- Hypotension
- Hypoxia

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[c]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Reprinted from Lee DW, 2019

Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638

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Management

When to start pharmacotherapy

- Please note that every product provides direction on when to initiate pharmacotherapy treatment based off their specific agent

Tocilizumab (Actemra®)

- Dose (Max – 800 mg dose)
  - < 30 kg: 12 mg/kg IV over 1 hr
  - >30 kg: 8 mg/kg IV over 1 hr
- No resolution in 8-24 hrs --> Up to 3 more doses can be given
- Note – Doses must be 8 hrs a part

Corticosteroids

- Options:
  - Dexamethasone 10 mg every 6 hrs
  - Methylprednisolone 1 mg/kg every 12 hr
- Note: Perform rapid taper

Neelapu SS et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62. Actemra [package insert]. South San Fransico, CA: Genetech; Updated December 2022.

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Tocilizumab (Actemra®)

MOA	BBW	ADEs	Clinical Pearls
Blocks IL-6 through binding with Il-6 receptors	Risk of serious infection	Significant: GI perforation, hematologic effects, hypersensitivity reactions, hepatic effects, and infection Common (>30%): Increased AST and injection site reaction	Approved for CRS treatment in August 2017 No renal or hepatic adjustments needed

MOA: Mechanism of Action, BBW: Black Box Warning
Actemra [package insert]. South San Fransico, CA: Genetech; Updated December 2022.

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Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Definition
Pathophysiology
Presentation
Diagnosis
Grading
Management

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Definition

ASTCT

- Reaction to immune therapy that leads to activation of immune cells which affects the central nervous system. Symptoms tend to be progressive and can include seizures, motor weakness, impaired consciousness, aphasia and/or cerebral edema.

Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

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Pathophysiology

Unclear, Proposed Mechanism

- Cytokine mediated endothelial activation → Clotting, leaky capillary, and blood brain barrier (BBB) disruption → systemic cytokines in CSF

Risk Factors

- Lymphodepletion with cyclophosphamide/fludarabine
- Early systemic inflammation
- High disease burden
- Present CRS (early/severe)

CSF: Cerebral Spinal Fluid
Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638; Santomasso BD et al. *Cancer Discov.* 2018;8(8):958-971.

45

Presentation

Symptoms

- Early Symptoms:
  - Dysgraphia, impaired attention, tremor, mild fatigue, and apraxia
    - Very specific symptom: Expressive aphasia
- Progression:
  - Global aphasia, seizures, altered consciousness, and/or coma

Onset

- Early – At same time as CRS symptoms (within 5 days)
- Late – After CRS resolution
- Delayed – Up to 3-4 weeks after immune effector cell-engaging therapy

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638; Santomasso BD et al. *Cancer Discov*. 2018;8(8):958-971.

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Diagnosis

Labs

- Increased CSF cytokines
- Disseminated Intravascular Coagulation → Increased PT, aPTT, and D-dimer
- Thrombocytopenia
- Increased overall cytokines in blood
- Increased CRP and Ferritin

Imaging/Procedures

- Electroencephalogram (EEG) - helps rule out seizures
- LP – Shows cytokines in CSF
- CNS Imaging

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638; Neelapu SS et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62. Santomasso BD et al. *Cancer Discov*. 2018;8(8):958-971.

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Grading

Pieces

- Encephalopathy
- Consciousness
- Seizure
- Motor Weakness
- Cerebral edema

ICE

- **Orientation:** orientation to year, month, city, hospital: 4 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

Reprinted from Lee DW, 2019

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[b]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[c]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Reprinted from Lee DW, 2019
Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638

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Management

When to start pharmacotherapy

- Every product provides direction on when to initiate pharmacotherapy treatment based off the specific agent

First line = Corticosteroids	Avoid Tocilizumab (Actemra®) unless concurrent CRS
• Crosses the BBB	• Does not Cross BBB • May worsen ICANS due to increasing IL-6 levels in CSF

Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638; SantomassoBD et al. *Cancer Discov*. 2018;8(8):958-971; *Karschnia P et al. Blood. 2019;133(20):2212-2221*; Brudno JN et al. *Blood*. 2016;127(26):3321-3330.

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CRS and ICANS

Refractory Management
Prevention
Anakinra (Kineret)
Literature Review

50

Refractory Management

Definition

- CRS remains unresolved or progresses after tocilizumab and maxed out corticosteroids
  - Max: Dexamethasone 10 mg IV every 6 hrs

Risk Factors

- High tumor burden
- Highly proliferative cancers

Treatment

- Anakinra (Kineret®)
  - Dose (CRS specific)
    - IV – 2 mg/kg/hr continuous for ≤ 72 hrs or 2-10 mg/kg/day in 2-4 divided doses
    - SQ – 2-10 mg/kg/day in 2-4 divided doses

SQ: Subcutaneous
Jain M et al. Blood. 2023; 141 (20): 2430–2442; Kineret [package insert]. Stockholm, Swedan: Swedish Orphan Biovitrum AB; Updated December 2020.

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Prevention

Candidates

- Rapid growing cancers
  - LBCL and B-ALL

Treatment

- Potentially debulking patients
  - Surgery and/or radiation
- Anakinra (Kineret®) 100 mg SQ every 12 hrs

Jain M et al. Blood. 2023; 141 (20): 2430–2442; Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; Updated December 2020; Park JH et al. *Blood*. 2021;138:96.

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Anakinra (Kineret®)

MOA	BBW	ADRs	Clinical Pearls
Blocks IL-1 through binding to IL-1 receptors	Risk of serious infections	**Common (>5%)**: Increased potassium/sodium, acute kidney injury, hypothermia, anxiety, and constipation	Especially useful in ICANS due to ability to cross BBB Dose adjustments not provided due to lack of studies in CRS/ICANS patients with hepatic or renal impairment

Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; Updated December 2020.

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Literature Review

Gazeau et al → Refractory Management

- Retrospective review of 43 patients with B cell or plasma cell cancers with refractory ICANS and/or CRS
- Anakinra >200 mg IV daily dose had lower treatment related mortality compared to 100 – 200 mg daily
- Anakinra related ADEs include hematoma and increased LFTs
- High dose anakinra was associated with faster ICANS and CRS resolution with lower treatment related mortality

Park et al → Prevention

- 31 patients with LBCL and MCL who received CAR-T therapy
- Efficacy of anakinra 100 mg SQ every 12 hours for duration of ≥ 10 days to prevent CRS and/or ICANS
- ORR 74% at 1 month and CRR 58% at month one and 52% at month 3
- Anakinra appears to be safe and effective at reducing the rate of severe ICANS and CRS

Gazeau N et al. *Transplant Cell Ther*. 2023;29(7):430-437; Park JH et al. *Blood*. 2021;138:96.

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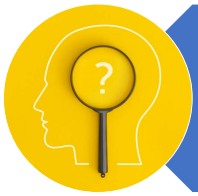
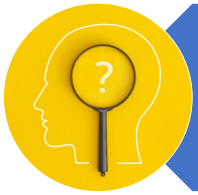
Question #3



CAR T-cell therapy can have serious nervous system side effects in some patients. (True/False)

55

Question #3



CAR T-cell therapy can have serious nervous system side effects in some patients. (True/False)

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CAR-T Summary

Pharmacist's Role
Future Directions
Summary

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Pharmacist's Role

REMS Program

- Hospital Enrollment
- All staff with CAR T-cell therapy touchpoints must complete training through the rems program and training records must be stored
- Maintain ≥ 2 doses Tocilizumab (Actemra®) per patient receiving CAR T-cell therapy
- Inform patient they must remain ≤ 2 hours away from the administering facility

Counseling on ADEs

- Watch for CRS and ICANS after discharge from administering facility
- Common ADEs: Fever, muscle pain, infection, BMS, HA, GI upset, and fatigue

Carvykti [package insert]. Somerset, NJ: Janssen Biotech; Updated February 2023; Abecma [package insert]. Summit, NJ: Celgene Corporation; Updated October 2022; Yescarta [package insert]. Santa Monica, CA: Kite Pharma; Updated April 2022; Breyanzi [package insert]. Bothell, WA: Juno Therapeutics; Updated June 2023;Tecartus [package insert]. Santa Monica, CA: Kite Pharma; Updated August 2023; Kymriah [package insert]. Morris Plains, NJ: Novartis; Updated August 2023.

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Pharmacist's Role

Effectiveness and safety of vaccinations post CAR T-Cell therapy unknown

- Expert opinions for CD19 CAR T-cell therapies patients:
  - In flu reason, receive flu vaccine ≥ 2 weeks prior to lymphodepleting regimen prior to CAR-T cell infusion
  - Wait 6 months after CAR-T cell infusion before receiving inactive vaccinations
  - Wait 12 months after CAR-T cell infusion before receiving live vaccinations

Hill JA et al. *Blood.* 2020;136(8):925-935.

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Summary

- CAR T-cell therapy is a living drug that targets either tumor antigen CD19 or BCMA
- FDA approved CD19 CAR T-cell therapies include Tisagenleceucel (Kymriah®), Axicabtagene Ciloleucel (Yescarta®), Brexucabtagene Autoleucel (Tecartus®), and Lisocabtagene Maraleucel (Breyanzi®)
- FDA approved BCMA CAR T-cell therapies include Idecabtogene Vicleucel (Abecma®) and Ciltacabtagene Autoleucel (Carvykti®)
- Common and potential life-threatening complications of CAR-T therapy include infections, CRS, and ICANS

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CAR-T Cell Therapy

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Updates on HIV Pharmacologic Therapies

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Nova Southeastern University
January 20th, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

Learning Objectives

- Discuss background and pathophysiology of human immunodeficiency virus (HIV)
- Evaluate screening and diagnostic methods for patients with HIV
- Analyze current practice guidelines and treatment options for patients living with HIV
- Identify clinical guideline updates in HIV management

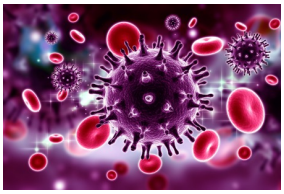
2

Abbreviations & Acronyms Used

- Human immunodeficiency virus (HIV)
- CD4+ T-Cells (Cluster of differentiation thymus lymphocytes)
- Centers for Disease Control (CDC)
- Sexually transmitted infections (STIs)
- Sexually transmitted diseases (STDs)
- Acquired immunodeficiency syndrome (AIDS)
- Antiretroviral therapy (ART)
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Integrase strand transfer inhibitors (INSTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Cardiovascular disease (CVD)
- Pre-exposure prophylaxis (PrEP)
- Post-exposure prophylaxis (PEP)
- Pneumocystis jirovecii pneumonia (PJP or PCP)
- Mycobacterium avium complex (MAC)

3

Background



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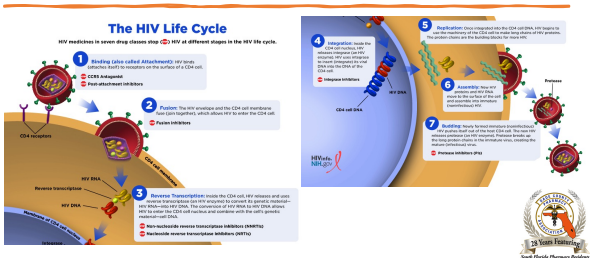
HIV Replication



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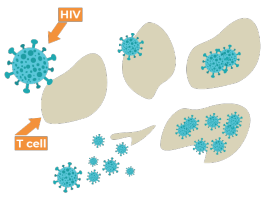
HIV-Mediated T-Cell Death



Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections. Front Immunol. 2017
6

6

Transmission

Semen

Vaginal/Rectal Secretions

Blood

Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections. *Front Immunol.* 2017

7

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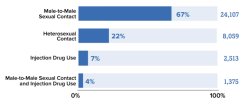
Epidemiology

New HIV Diagnoses in the US and Dependent Areas by Transmission Category, 2021*



NOTE: Does not include other and perinatal transmission categories.

* Among people aged 13 and older.

Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2021. HIV Surveillance Report 2023;34.

Basic Statistics | HIV Basics | HIV/AIDS | CDC. 2023

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8

Screening & Diagnosis

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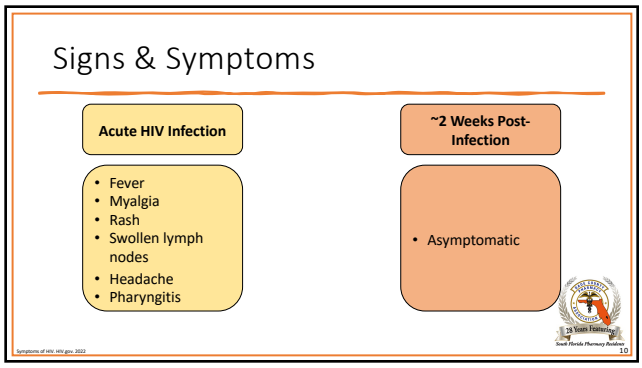
Signs & Symptoms
Acute HIV Infection
• Fever
• Myalgia
• Rash
• Swollen lymph nodes
• Headache
• Pharyngitis
~2 Weeks Post-Infection
• Asymptomatic
Symptoms of HIV. HIV.gov. 2022
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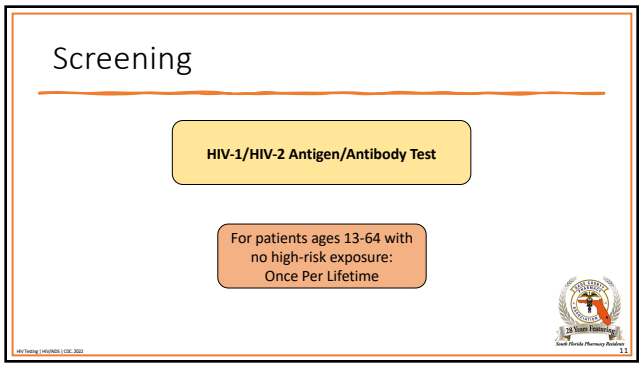
Screening
HIV-1/HIV-2 Antigen/Antibody Test
For patients ages 13-64 with no high-risk exposure:
Once Per Lifetime
HIV Testing | HIV/AIDS | CDC. 2022
11

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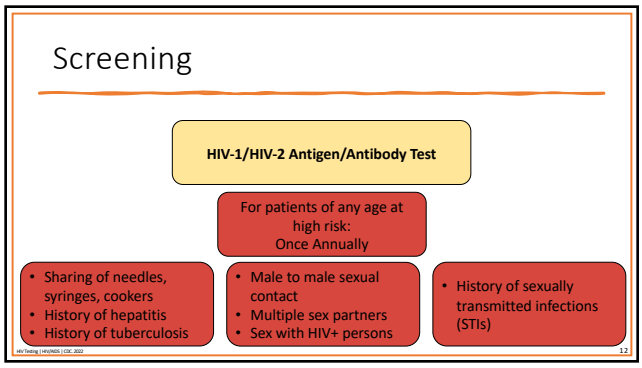
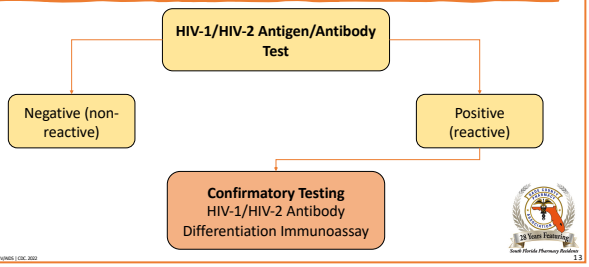

Screening
HIV-1/HIV-2 Antigen/Antibody Test
For patients of any age at high risk:
Once Annually
• Sharing of needles, syringes, cookers
• History of hepatitis
• History of tuberculosis
• Male to male sexual contact
• Multiple sex partners
• Sex with HIV+ persons
• History of sexually transmitted infections (STIs)
HIV Testing | HIV/AIDS | CDC. 2022
12

12

Diagnosis



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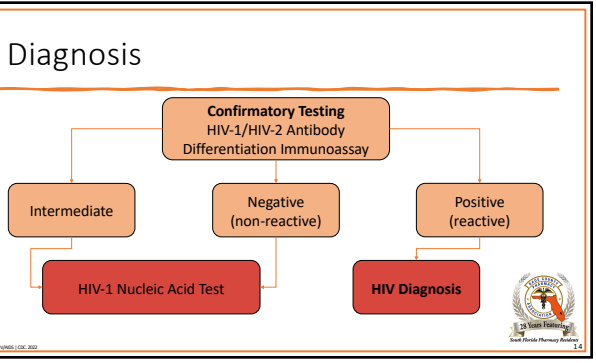
Diagnosis



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Treatment & Prevention

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Monitoring & Treatment Goals

CD4+ T-cell Count

HIV Viral Load

Treatment Goal

Undetectable HIV Viral Load (< 50 copies/mL)

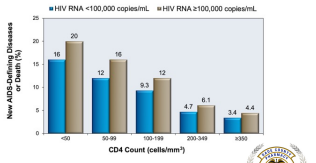
16

Antiretroviral Therapy (ART)

ART should be started in ALL patients with HIV

ART suppresses HIV viral load

Adherence is crucial



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Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Drug Name	Formulation & Route	Mechanism of Action	Dose (in combination with other ARTs)
Ziagen (abacavir)	Oral tablet	Competitively inhibits reverse transcriptase, preventing conversion of HIV RNA to DNA	600mg PO daily
Emtriva (emtricitabine)	Oral capsule Oral solution		200mg PO daily
Epivir (lamivudine)	Oral tablet Oral solution		300mg PO daily
Viread (tenofovir disoproxil fumarate) [TDF]	Oral tablet Oral powder		300mg PO daily
Biktarvy* (tenofovir alafenamide) [TAF]	Oral tablet		25mg PO daily
Retrovir (zidovudine)	Oral capsule, tablet Intravenous solution		300mg PO BID

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Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Drug Name	Warnings & Precautions	Side Effects	Clinical Pearls
Ziagen (abacavir)	Lactic acidosis and hepatomegaly with steatosis Acute HBV reactivation with discontinuation of emtricitabine, TAF, and TDF	Nausea Diarrhea Headaches Hepatotoxicity (increase in LFTs)	**Boxed warning**: severe rash (HLA-B*5701 allele)
Emtriva (emtricitabine)			Hyperpigmentation in the palms of the hands or soles of the feet
Viread (tenofovir disoproxil fumarate) [TDF]			Renal impairment (more with TDF) Decreases bone mineral density
Biktarvy* (tenofovir alafenamide) [TAF]			Lipid abnormalities
Retrovir (zidovudine)			Neutropenia and anemia, Myopathy

Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy–Naive Patients | Clinicalinfo.HIV.gov. 2021

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Integrase Strand Transfer Inhibitors (INSTIs)

Drug Name	Formulation & Route	Mechanism of Action	Dose (in combination with other ARTs)
Biktarvy* (bictegravir)	Oral tablet	Inhibits integrase, preventing HIV DNA from integrating into the host cell DNA strand	50mg PO daily
Tivicay (dolutegravir)	Oral tablet		50mg PO daily
Genvoya*, Stribild* (elvitegravir)	Oral tablet		150mg PO daily
Isentress (raltegravir)	Oral tablet, chewable tablet		400mg PO BID

Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy–Naive Patients | Clinicalinfo.HIV.gov. 2022

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Integrase Strand Transfer Inhibitors (INSTIs)

Drug Name	Warnings & Precautions	Side Effects	Clinical Pearls
Biktarvy* (bictegravir)	N/A	Headache Insomnia Diarrhea Weight gain	Increases serum creatinine
Tivicay (dolutegravir)	Risk of depression and suicidal ideation		Small risk of neural tube defects
Genvoya*, Stribild* (elvitegravir)			Can cause proteinuria
Isentress (raltegravir)			Myopathy, rhabdomyolysis

Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy–Naive Patients | Clinicalinfo.HIV.gov. 2022

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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug Name	Formulation & Route	Mechanism of Action	Dose (in combination with other ARTs)
Sustiva (efavirenz)	Oral capsule, tablet	Non-competitively inhibits reverse transcriptase, preventing conversion of HIV RNA to DNA	600mg PO daily
Edurant (rilpiverine)	Oral tablet		25mg PO daily
Viramune XR (nevirapine)	Oral extended-release tablet, oral suspension		200mg IR PO daily for 14 days followed by 400mg XR PO daily

Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug Name	Warnings & Precautions	Side Effects	Clinical Pearls
Sustiva (efavirenz)	Hepatoxicity Stevens-Johnson syndrome (SJS)/toxic epidermal(TEN) necrolysis (mostly with nevirapine)	Depression, suicidal thoughts CNS depression	Can increase total cholesterol and triglycerides
Edurant (rilpiverine)			Contraindicated with PPIs, separate from H2RAs and antacids Do not use if viral load > 100,000 copies/mL and/or if CD4 count < 200 cells/mm³
Viramune XR (nevirapine)			Rhabdomyolysis

Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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Protease Inhibitors (PIs)

Drug Name	Formulation & Route	Mechanism of Action	Dose (in combination boosters)
Prezista (darunavir)	Oral tablet, oral suspension	Inhibits HIV protease, preventing viral protein from breaking down into mature, infectious protein chains	800mg PO daily
Reyataz (atazanavir)	Oral capsule		300mg PO daily

Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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Protease Inhibitors (PIs)

Drug Name	Warnings & Precautions	Side Effects	Clinical Pearls
Prezista (darunavir)	Metabolic abnormalities Increased CVD risk Hepatotoxicity SJS/TEN	Angioedema Diarrhea Nausea	Caution with sulfa allergy Strong CYP3A4 inhibitor
Reyataz (atazanavir)			Hyperbilirubinemia Requires acidic gut for absorption Strong CYP3A4 inhibitor

Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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Pharmacokinetic Boosters

Drug Name	Formulation & Route	Mechanism of Action	Dose
Norvir (ritonavir)	Oral tablet, oral solution	Inhibitors of CYP3A4, inhibiting ART metabolism leading to boosted ART levels and therapeutic effects	100 – 400mg PO daily
Tybost (cobicistat)	Oral tablet		150mg PO daily

Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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Pharmacokinetic Boosters

Drug Name	Warnings & Precautions	Side Effects	Clinical Pearls
Norvir (ritonavir)	SJS/TEN Hepatotoxicity Increase in total cholesterol	Weight gain Rash Jaundice	Cannot be used together and are not interchangeable Some antiretroviral activity provided with ritonavir, none observed with cobicistat
Tybost (cobicistat)	Renal toxicity		

Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. 2021

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First-Line ART Regimens

Biktarvy	bictegravir [INSTI] + emtricitabine [NRTI] + TAF [NRTI]
Triumeq	dolutegravir [INSTI] + abacavir [NRTI] + lamivudine [NRTI]
Dovato	dolutegravir [INSTI] + lamivudine [NRTI]

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Single Tablet Regimens

Drug Name	Clinical Pearls
Biktarvy	**Boxed warning:** hepatitis B exacerbation in patients with HIV-1 and HBV coinfection Contains TAF, do not initiate in CrCl < 30 mL/min
Triumeq	Contains abacavir, must test for HLA-B*5701 allele before initiating
Dovato	Do not use in treatment-naïve patients if viral load is > 500,000 copies/mL or there is known hepatitis B co-infection

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First-Line ART Regimens

Tivicay + Truvada	dolutegravir [INSTI] + emtricitabine [NRTI] + TDF [NRTI]
Tivicay + Descovy	dolutegravir [INSTI] + emtricitabine [NRTI] + TAF [NRTI]

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Other Combination ART Products

Stribild	elvitegravir [INSTI] + cobicistat [booster] + emtricitabine [NRTI] + TDF [NRTI]
Atripla	efavirenz [NNRTI] + emtricitabine [NRTI] + TDF [NRTI]
Symtuza	darunavir [PI] + cobicistat [booster] + emtricitabine [NRTI] + TAF [NRTI]

Antiretroviral Medications and Initial Therapy. National HIV Curriculum. 2023

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Pre-Exposure Prophylaxis (PrEP)

Truvada	emtricitabine [NRTI] + TDF [NRTI]
Descovy	emtricitabine [NRTI] + TAF [NRTI]
Apretude	cabotegravir [INSTI]

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE. 2021

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Post-Exposure Prophylaxis (PEP)

Occupational	**Non-Occupational**
• Exposure typically related to healthcare worker accidental contact with bodily fluids via needlestick	• Exposure due to unprotected sex, injection drug use

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE. 2021

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Post-Exposure Prophylaxis (PEP)

Occupational

Non-Occupational

Treatment for both started within 72 hours of exposure and continued for 28 days

Truvada + Tivicay or Isentress

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE. 2021

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Acquired Immunodeficiency Syndrome (AIDS)

CD4+ T-cell count < 200 cells/mm^3
OR
Development of AIDS-related conditions

- Opportunistic Infections
- Cancer
- HIV Wasting Syndrome

The Stages of HIV Infection | NIH. 2021

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Updates in HIV Management

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Updates in HIV Management

Drug Name	Formulation & Route	Mechanism of Action	FDA Approval
Sunlenca (lenacapavir)	Subcutaneous injection once every 6 months	HIV-1 capsid inhibitor, blocks HIV-1's assembly of its protein capsid and interferes with other steps in HIV replication	Approved for adults with HIV that have previously failed ART due to resistance, intolerance, or non-adherence Must be given with other ART

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. 2023

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Updates in HIV Management

Drug Name	Manufacturer	Trial Dosing Regimen
Sunlenca (lenacapavir)	Gilead	36 participants were randomly assigned in a 2 to 1 ratio to receive oral lenacapavir (600mg days 1 and 2; 300mg through day 8) or placebo additional to existing failing regimen At day 15, those on PO lenacapavir received 927mg subcutaneously every 26 weeks and those on placebo were initiated on lenacapavir, beginning with PO phase Within cohort 1, 30 out of 36 participants had less than 50 HIV-1 RNA copies/mL at week 52

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. 2023

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Updates in HIV Management

Drug Name	Formulation & Route	Mechanism of Action	FDA Approval
Cabenuva (cabotegravir/ rilpivirine)	Intramuscular (IM) injection once a month or once every other month	As an INSTI, cabotegravir inhibits HIV integrase, blocking the strand transfer of retroviral DNA integration As a NNRTI, rilpivirine non-competitively inhibits reverse transcriptase, preventing conversion of HIV RNA to DNA	Approved for treatment of HIV-1 in virologically suppressed (HIV RNA < 50 copies/mL) adults and adolescents ≥ 12 years of age weighing ≥ 35kg with no history of treatment failure to replace current ART

Cabenuva (cabotegravir and rilpivirine) [prescribing information]. Durham, NC: GlaxoSmithKline. 2021

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Updates in HIV Management

Drug Name	Manufacturer	Dosing
Cabenuva (cabotegravir/ rilpivirine)	GlaxoSmithKline	Monthly Injection: • Initiation: cabotegravir 600mg/rilpivirine 900mg IM once monthly • Continuation: cabotegravir 400mg/rilpivirine 600mg IM once monthly up to 7-days before or after scheduled follow-up dose Every 2 Months Injection: • Initiation: cabotegravir 600mg/rilpivirine 900mg IM once monthly for two doses • Continuation: cabotegravir 600mg/rilpivirine 900mg IM once every two months up to 7-days before or after scheduled follow-up dose

Cabenuva (cabotegravir and rilpivirine) [prescribing information]. Durham, NC: GlaxoSmithKline. 2021

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Quiz #1

Which of the following are possible mediums for transmission of HIV?
a)Mosquito bite
b)Semen
c)Sweat
d)Physical contact

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Quiz #1

Which of the following are possible mediums for transmission of HIV?
a)Mosquito bite
b)Semen
c)Sweat
d)Physical contact

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Quiz #2

After how much time post-exposure is it recommended to screen for HIV infection?

a)24 hours
b)72 hours
c)1 week
d)2 weeks

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Quiz #2

After how much time post-exposure is it recommended to screen for HIV infection?

a)24 hours
b)72 hours
c)1 week
d)2 weeks

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Quiz #3

A treatment naïve patient with HIV presents with a viral load of 673,000 cells/mL, which of the following first-line agents is contraindicated in this patient?

a)Biktarvy
b)Dovato
c)Triumeq
d)Tivicay + Descovy

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Quiz #3

A treatment naïve patient with HIV presents with a viral load of 673,000 cells/mL, which of the following first-line agents is contraindicated in this patient?

a)Biktarvy
b)Dovato
c)Triumeq
d)Tivicay + Descovy

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Conclusion

- HIV is a chronic condition that destroys host T-cells leading to worsening immune function over time
- HIV is most commonly transmitted through direct contact with bodily fluids such as semen, blood, vaginal/rectal secretions, and breast milk
- If left untreated, HIV can progress to AIDS and eventually death
- Combination ART is used for treatment and prevention of HIV
- First-line agents for treatment include Biktarvy, Triumeq, and Dovato
- Truvada, Descovy, and Apretude can be used for PrEP
- Truvada alongside Tivicay or Isentress can be used for PEP
- Sunlenca is reserved for refractory HIV infection, given in combination with other antiretrovirals
- Cabenuva is a once a month or once every 2 months long acting injectable used as monotherapy for HIV-1 infection

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10. Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. Published June 3, 2021. Accessed October 20, 2023. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/table-8c-characteristics-non-nucleoside
11. Table 8d. Characteristics of Protease Inhibitor Options That Are Recommended as Initial Therapy for People with HIV | Clinicalinfo.HIV.gov. Published June 3, 2021. Accessed October 20, 2023. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/table-8d-characteristics-protease

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Questions?

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Updates on HIV Pharmacologic Therapies

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Neurosyphilis: A Central Challenge

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January 20th, 2024

Objectives

- Review pathophysiology, epidemiology, clinical presentation, relevant laboratory data, and symptoms assessment in neurosyphilis
- Discuss the risk factors and general management of neurosyphilis
- Summarize pharmacologic management based on disease manifestation

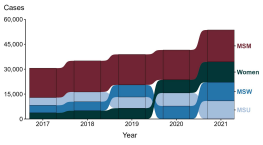
Introduction

- "Neurosyphilis" refers to infection of the central nervous system (CNS) by *Treponema pallidum*
- Neurosyphilis can occur at any time after initial infection.
- Early neurosyphilis most commonly involves the cerebrospinal fluid, meninges, and vasculature
- Late neurosyphilis most commonly involves the brain, and spinal cord parenchyma (general paralysis of the insane and tabes dorsalis)

Ropper A. *N Engl J Med.* (2019) 381:2377

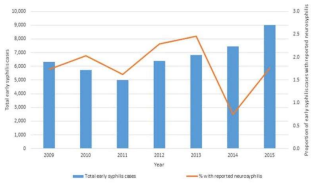
Epidemiology

- In 2021, 176,713 cases of syphilis were reported, including 53,767 cases of primary and secondary (P&S) syphilis, the most infectious stages of the disease.
- Men Who Have Sex with Men (MSM) are disproportionately impacted by syphilis, accounting for almost half (46.5%) of all male P&S syphilis cases in 2021
- Among women, rates have increased 55.3% during 2020 to 2021 and 217.4% during 2017–2021, highlighting the sustained increase in the heterosexual syphilis epidemic in the United States.



CDC, National Overview of STDs, 2021

Epidemiology



* Includes 10 states (Delaware, Georgia, Hawaii, Indiana, Kentucky, Maine, South Dakota, Texas, Virginia, and West Virginia) that consistently reported a response for neurologic involvement for ≥ 70% of early syphilis cases from 2009–2015. Reporting percentage completeness ranged from 74% to 100% for these 10 states across the time period.

- National epidemiology of neurosyphilis (including ocular and otosyphilis)
  - Low overall prevalence: 0.84% from 2009-2015
  - Very difficult to track
  - Under diagnosed
  - Under reported/ lack of reporting

De Voux A, et al. *Sex Transm Dis*. 2018 Jan;45(1):39-41.

Microbiology

- *Treponema pallidum* is a highly infectious bacteria that spreads systemically within minutes of infection, resulting in syphilis
- Approximately 10 to 13 microns long but only 0.15 microns in width making it too slender to be visualized by direct microscopy
- The organism can be seen with darkfield microscopy, When visualized by this method, *T. pallidum* is a delicate, corkscrew-shaped organism with tightly wound spirals

Mushet DM, et al. *McGraw-Hill, New York* 1990. p.205.

Pathophysiology

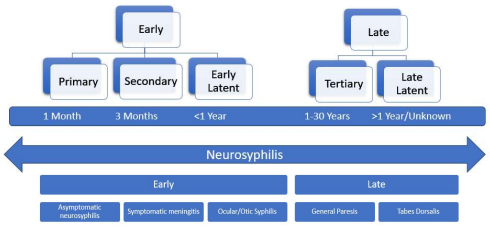
- Infection occurs via penetration of the spirochete through mucosal membranes as well as epithelial breaks in the skin.
- CNS invasion and neurological complications can occur during any stage of the infection
- Unlike other bacteria that can infect the cerebrospinal fluid (CSF), invasion of CSF with *T. pallidum* does not always result in persistent infection, as spontaneous resolution may occur in some cases without an inflammatory response. In other cases, spontaneous resolution may occur after a transient meningitis

Ropper A. *N Engl J Med.* (2019) 381:2377

Which bacterium is responsible for causing syphilis, including neurosyphilis?

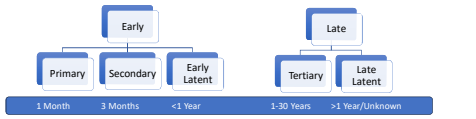
A. *Chlamydia trachomatis*
B. *Mycobacterium tuberculosis*
C. *Treponema pallidum*
D. *Neisseria gonorrhoeae*

Stages of Syphilis



Ropper A. *N Engl J Med.* (2019) 381:2377

Stages of Syphilis: Primary

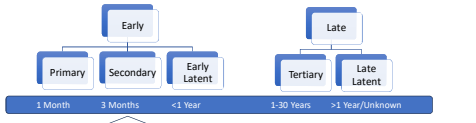


- **Chancre (ulcer):** Single, painless, indurated, clean-based lesion with rolled edge
- It often goes unrecognized, especially in the rectal or vaginal area
- May have associated regional lymphadenopathy

Neurosyphilis

Ropper A. *N Engl J Med.* (2019) 381:2377

Stages of Syphilis: Secondary



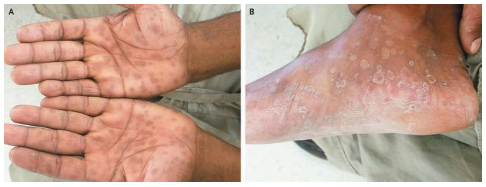
- **Body rash:** often involves palms/soles
- Generalized lymphadenopathy
- Constitutional symptoms
- Mucous patches
- Condyloma lata
- Patchy alopecia

Neurosyphilis

Ropper A. *N Engl J Med.* (2019) 381:2377

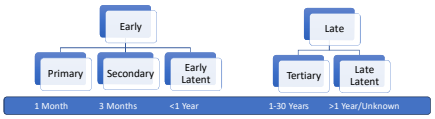
Secondary Syphilis

Rash associated with secondary syphilis



Badri T. et al. *N Engl J Med.* (2011) 364:71

Stages of Syphilis: Early Latent

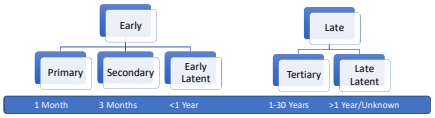


- **Within first year of infection:**
- Positive serologic testing
- No symptoms

Neurosyphilis

Ropper A. *N Engl J Med.* (2019) 381:2377

Stages of Syphilis: Tertiary



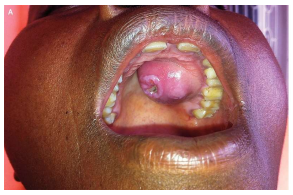
- **Cardiovascular:**
  - Aortitis, thoracic aortic aneurysm
- **Gummatous:**
  - Nodular lesions in bone, skin, etc.

Neurosyphilis

Ropper A. *N Engl J Med.* (2019) 381:2377

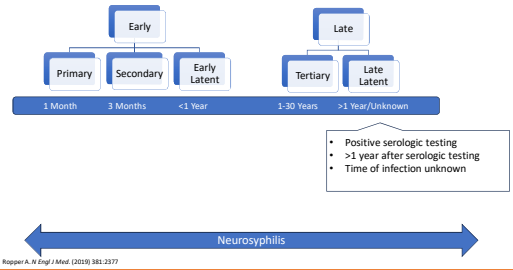
Tertiary Syphilis

Syphilitic Gumma



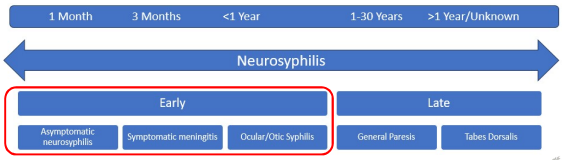
Cherniak W. et al. *N Engl J Med.* (2014) 371:667

Stages of Syphilis: Late Latent



Ropper A. *N Engl J Med.* (2019) 381:2377

Clinical Manifestations: Neurosyphilis



Ropper A. *N Engl J Med.* (2019) 381:2377

Clinical Manifestations of Early Neurosyphilis

- Asymptomatic neurosyphilis:
  - No signs or symptoms of central nervous system disease, although they may have evidence of concomitant primary or secondary syphilis.
  - Asymptomatic neurosyphilis can occur within weeks to months after infection, but less commonly occurs more than two years after infection.
  - Diagnosis based on the identification of CSF abnormalities.
  - Patients with asymptomatic neurosyphilis, should be treated to prevent disease progression

Ropper A. *N Engl J Med.* (2019) 381:2377

Clinical Manifestations of Early Neurosyphilis

- Symptomatic meningitis:
  - Most often, occurs within the first year after infection, but it can occur years later. As with peripheral findings of early syphilis may coexist, particularly the rash of secondary disease.
  - Patients with symptomatic syphilitic meningitis complain of headache, confusion, nausea and vomiting, and stiff neck.
  - Visual acuity may be impaired if there is concomitant uveitis, retinitis, or optic neuropathy. Signs include cranial neuropathies, particularly of the optic, facial, or auditory nerves.
  - The CSF abnormalities that accompany symptomatic meningitis are more prevalent than those seen in asymptomatic meningitis.

Ropper A. *N Engl J Med.* (2019) 381:2377

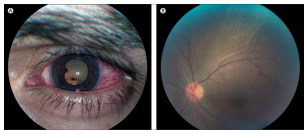
Patient NS

- 56 years old woman HIV-infected (last CD4 716 cells/mm3 two years prior, on BIC/FTC/TAF), who presents with **bilateral eye pain**, **redness**, **photosensitivity**, **vision loss**, retro-orbital headache, and **bilateral tinnitus.**
  - First developed a **rash** over her legs, palms, and soles about a month earlier, and noticed (at the same time) some flat painless lesions on her genitals.

(She was seen in the ED previously and was diagnosed with "conjunctivitis" and sent home)

Clinical Manifestations of Early Neurosyphilis

- Ocular syphilis:
  - Ocular syphilis can involve almost any eye structure, but posterior uveitis is the most common and present with diminished visual acuity.
  - Additional manifestations may include optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis.



Anderson AM, et al. *Lancet.* (2009); 9(7): 453

Clinical Manifestations of Early Neurosyphilis

- Otosyphilis:
  - Hearing loss, with or without tinnitus, should be considered as part of the neurologic symptoms or signs of neurosyphilis.
  - Like ocular syphilis, hearing loss may or may not be accompanied by meningitis.

Oliver S, et al. *Sex Transm Dis* 2016; 43:524.

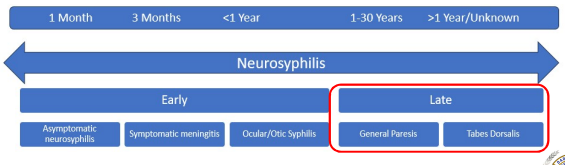
Clinical Manifestations of Early Neurosyphilis

- Meningovascular syphilis:
  - Syphilitic meningitis may affect any vessel in the subarachnoid space surrounding the brain or spinal cord and result in thrombosis, ischemia, and infarction.
  - Prodromal symptoms: headache, dizziness, or personality changes, for days or weeks before the onset of ischemia or stroke.
  - The manifestations of cerebral ischemia may be acute or chronic.
  - The middle cerebral artery and its branches are most affected.

Oliver S, et al. *Sex Transm Dis* 2016; 43:524.

Clinical Manifestations of Late Neurosyphilis

- Late neurosyphilis manifestations are considered "tertiary" forms of neurosyphilis:



Osman C, et al. *N Engl J Med* 2016; 375:a40

Clinical Manifestations of Late Neurosyphilis

- **General paresis:**
  - Also known as dementia paralytica, is a progressive dementing illness.
  - Usually develops 10 to 25 years after infection, but it can occur as early as two years after infection.
  - In the early stage of disease, general paresis is associated with symptoms of forgetfulness and personality change.
  - While the neurologic examination may be normal in some patients with general paresis, common abnormal findings include dysarthria, facial and limb hypotonia, intention tremors of the face, tongue, and hands, and reflex abnormalities.

Osman C, et al. *N Engl J Med* 2016; 375:e40

Clinical Manifestations of Late Neurosyphilis

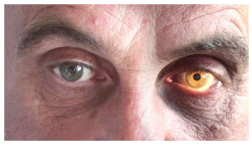
- **Tabes dorsalis:**
  - Also called locomotor ataxia, is a disease of the posterior columns of the spinal cord and of the dorsal roots.
  - Longest latent interval between primary infection and onset of symptoms of all forms of neurosyphilis, with an average of about 20 years.
  - Characterized by sudden, brief, severe stabs of pain that may affect the limbs, back, or face and that may last for minutes or days.

Osman C, et al. *N Engl J Med* 2016; 375:e40

Argyll-Robertson Pupil

Present in almost one-half of Tabes Dorsalis patients:

- Small pupils
- Doesn't respond to light
- Contracts normally to accommodation
- Dilates imperfectly to mydriatics
- Does not dilate in response to painful stimuli



Osman C, et al. *N Engl J Med* 2016; 375:e40

Syphilis Serologies

Non-treponemal tests

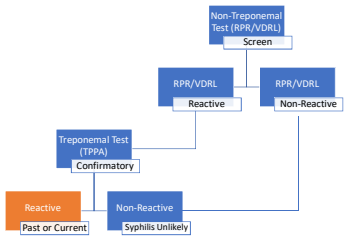
- Examples: **RPR and VDRL**
- Quantitative tests: allow for assessment of disease burden, treatment adequacy, and re-infection

Treponemal tests

- Examples: **TPPA, TPHA, FTA-ABS, EIA, CIA**
- Detect antibodies specific to *T. Pallidum*
- Antibodies usually stay positive for life after initial infection
- Not quantitative; cannot be used to assess for reinfection or response to treatment

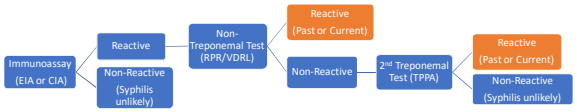
Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Serologic Screening for Syphilis: Traditional Algorithm



Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Serologic Screening for Syphilis: Reverse Algorithm



Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Non-Treponemal (RPR/VDRL) Titers

- Higher numbers correspond to higher level of antibodies in patient's serum.
- **Two-fold change:** Generally considered within margin of error of test.
- **Four-fold change:** Sustained for at least 2 weeks considered to be significant.
- Compare titers using same serologic test: RPR often higher than VDRL

1:1024
1:512
1:256
1:128
1:64
1:32 — 2-fold change
1:16
1:8
1:4 — 4-fold change
1:2
1:1

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Back to Patient NS

- She was seen by ophthalmologist and diagnosed with **anterior uveitis**
- Laboratory tests:
  - **RPR 1:64; CIA Reactive**
- **Early syphilis** (secondary lesions one month earlier)
- **Neurosyphilis** (headache with/without photophobia)
- **Ocular syphilis** (bilateral redness and decreased vision)
- **Otosyphilis** (tinnitus)

Will a CSF examination change treatment recommendations?

Diagnosis of Neurosyphilis

No one single test can diagnose; depends on a combination of:

- Neurologic signs and symptoms
- Consistent serologies

(note: RPR may be non-reactive in a portion of late NS)

- CSF:
  - Venereal Disease Research Laboratory (VDRL) is highly specific but insensitive
  - **For a person with neurologic signs or symptoms , a reactive CSF-VDRL is considered diagnostic of neurosyphilis**
  - Elevated protein
  - Lymphocytic pleocytosis

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Diagnosis of Ocular and Otosyphilis

Ocular syphilis

- Ocular symptoms, consistent serologies
- Abnormal slit lamp exam. Co-manage with ophthalmologist
- CSF:
  Same as neurosyphilis, but nearly 40% will have no CSF abnormalities.
  (CSF exam not required for diagnosis)

Otosyphilis

- Otic symptoms, consistent serologies
- Abnormalities on ENT exam/testing: Co-manage with otolaryngology
- CSF:
  Same as neurosyphilis, but nearly 90% will have no CSF abnormalities.
  (CSF exam not required for diagnosis)

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Who needs an LP looking for Neurosyphilis?

Perform a lumbar puncture (LP) in persons who:

- Have neurological signs and symptoms
  (not required in those with isolated ocular or otic symptoms)
- Diagnosed with tertiary syphilis (cardiovascular, gummas)
- Those that signs/symptoms persist or recur or with a 4-fold increase after treatment but not reported sexual exposure during the last 3-6 months or year
- Consider in those with lack of 4-fold decline without sexual exposure in whom follow up is uncertain

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

What is the neurosyphilis hallmark CSF finding in patients with neurologic signs or symptoms?

A. Elevated protein levels
B. Decreased glucose levels
C. Presence of white blood cells
✓ D. Positive VDRL (Venereal Disease Research Laboratory) test

Treatment: Primary and Secondary Syphilis

Preferred:

- Penicillin G Benzathine 2.4 million units IM **once**

Alternatives (choose one):

- Doxycycline 100 mg orally twice daily for **14 days**
- Ceftriaxone 1 g daily IM or IV for **10 to 14 days**

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Treatment: Tertiary Syphilis

Preferred:

- Penicillin G Benzathine 2.4 million units IM **once weekly for three weeks**

Alternatives (choose one):

- Doxycycline 100 mg orally twice daily **for four weeks**
- Ceftriaxone 2 g daily IM or IV for **10 to 14 days**

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Treatment: Ocular, Otosyphilis and Neurosyphilis

Preferred:

- Aqueous penicillin G, **3 to 4 million units IV every four hours** (or 18 to 24 million units continuous IV infusion) for **10 to 14 days**
- **For patients with late neurosyphilis, consider giving an additional dose of penicillin G Benzathine (2.4 million units IM once) after completing IV therapy.**
- Oral penicillin is not recommended in any stage of syphilis.

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Treatment Alternative: Neurosyphilis

- **Alternative to IV therapy:**

  Penicillin G Procaine 2.4 million units IM once daily

  PLUS

  Probenecid 500 mg PO 4 times/day, both for 10-14 days

****Penicillin G Procaine discontinued worldwide****

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-4):39-59
Wheeler, M. (2023, June 13). ASHP. https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=240&loginreturnUrl=SSOCheckOnly

Treatment Alternative: Neurosyphilis

6/13/2023

Penicillin G Procaine Injection

Products Affected - Description

- Penicillin G procaine intramuscular injection, Pfizer, 600,000 units/mL, 1 mL syringe, 10 count, NDC 60793-0130-10 - discontinued
- Penicillin G procaine intramuscular injection, Pfizer, 600,000 units/mL, 2 mL syringe, 10 count, NDC 60793-0131-10 - discontinued

Estimated Resupply Dates

- Pfizer has discontinued penicillin G procaine 600,000 unit/mL 1 mL and 2 mL syringes.

Wheeler, M. (2023, June 13). ASHP. https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=240&loginreturnUrl=SSOCheckOnly

Patient NS: CSF Examination

- CSF: **63 WBC**, protein 121, **VDRL 1:2**
- In this case, CSF examination results would not change the treatment course

  Patient would need 14 days of IV penicillin irrespective of the CSF results because she has **ocular** and **otic** manifestations

Patient NS

- Patient was treated appropriately for 14 days with IV penicillin. The therapy would adequately cover:
  - Neurosyphilis
  - Ocular syphilis
  - Otosyphilis
- Even if her CSF examination had been normal, she would have required the same course because of the otic and ocular manifestations.

Penicillin Mechanism of Action

- Penicillin kills susceptible bacteria by specifically inhibiting the trans-peptidase that catalyzes the final step in cell wall biosynthesis, the cross-linking of peptidoglycan.
- Beta-lactam antibiotic, active against gram-positive cocci, including non-penicillin resistant streptococcal, staphylococcal, and enterococcal species.
- Has limited activity against gram negative aerobes.
- Penicillin G is active against certain spirochetes and is commonly used to treat syphilis. It is also employed for the treatment of skin and skin structure infections.

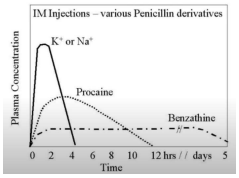
Yocum RR, et al. *J Biol Chem*. 1980 10;255(9):3977-86.

Penicillin Parenteral Formulations

- Penicillin G Benzathine (Bicillin®)
  - IM only
  - 2.4 million units of Benzathine ➡ low serum levels for > 7 days
- Penicillin G Procaine* **(No longer in the market)**
  - IM only
  - Levels for 24 hours
  - Typically dosed with probenecid to prolong duration of action
- Penicillin G, Aqueous, Crystalline
  - IV
  - Sodium or potassium salt forms available

Penicillin G Procaine. Prescriber Information. Pfizer; 2023
Penicillin G Benzathine. Prescriber Information. Pfizer; 2023
Penicillin G Sodium. Prescriber information. Pfizer; 2012

Penicillin Pharmacokinetics by Preparation



- *T. Pallidum* requires low concentrations of penicillin.
- A single shot of Benzathine provides levels over the MIC of the organism for 5 to 7 days.
- Procaine rapidly increases levels, but they go down after 12 hours, which is why is dosed once a day.
- IV delivers very high peak levels, used for neurosyphilis, which allows CNS penetration. Very short half-life, which means it has to be administered every 4 to 6 hours.

Kathrine MA, et al. *American Journal of Clinical Pathology* 18(5): 421-428

Treatment Alternative: Neurosyphilis

- **Penicillin allergy:**

Limited data indicate that **ceftriaxone 1–2 g daily either IM or IV for 10–14 days** can be used as an alternative treatment for persons with neurosyphilis

If concern exists regarding ceftriaxone safety for a patient with neurosyphilis, skin testing should be performed to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended.

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Treatment Alternative: Neurosyphilis

Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicenter study

- 208 neurosyphilis patients included in the study
  (42 in the ceftriaxone group vs 166 in the benzylpenicillin group)
- Clinical response in 41 patients (98%) ceftriaxone group vs 125 patients (76%) in benzylpenicillin (p=0.017)
- Serological response at 6 months did not differ between the groups (21 [88%] in ceftriaxone group vs 76 [82%] in benzylpenicillin group (p=0.50)
- Randomized, controlled trials should be done to confirm results.

Bettuzzi T, et al. *Lancet Infect Dis.* 2021 Oct;21(10):1441-1447.

Treatment: Pregnancy

- Penicillin G is the only known effective antimicrobial for treating fetal infection and preventing congenital syphilis
- Pregnant women should be treated with the recommended penicillin regimen for their stage of infection
- If history of penicillin allergy, they should be desensitized and treated with penicillin G
- Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

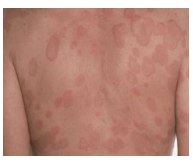
Penicillin Allergy

- Most identified drug allergy in medical records
- 80-90% of people who report a penicillin allergy not truly allergic. (Negative skin test)
- True incidence: ~10%
- Anaphylaxis: 1-5 patients/10,000

Salkind AR et al. JAMA. 2001;285(19):2498-2505.
Khan DA et al. J Allergy Clin Immunol. 2022;150(6):1333-1393.
Castells M et al. N Engl J Med. 2019;381:2338-2351.

Immediate Reactions (Type I)

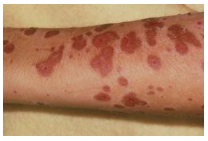
- IgE mediated
- Immediate onset: minutes to hours
- Can do skin test
- Clinical features:
  - Erythema
  - Laryngeal edema/bronchoconstriction
  - Urticaria/angioedema
  - Hypotension, cardiovascular collapse
- Do not rechallenge
- Avoid all beta-lactams



Blumenthal K et al. *Lancet*. 2019;393(10167):183-198.

Late Reactions

- >72 hours of exposure
- Not IgE mediated
- Type II: hemolytic anemia, thrombocytopenia
  - Associated with high doses
  - Reversible with drug withdrawal
  - Can re-occur when rechallenge
- Type IV: serum sickness
  - Malaise, fever, joint pain
- Steven-Johnson Syndrome
  - Can occur up to 1-3 weeks after drug administration
  - Exfoliative dermatitis, blister formation
  - Very rare, but can be fatal



Blumenthal K et al. *Lancet*. 2019;393(10167):183-198.
Zagaria MA. *US Pharm*. 2008;33(4):20-26.

Idiopathic Reactions

- "Ampicillin rash"
- Clinical features
  - Small, pink or red flat spots
  - Non-itchy
  - Resolves in its own
  - Can rechallenge
- Do NOT classify as a penicillin allergy
- Does not respond to diphenhydramine (no histamine release)
- Don't stop antibiotic

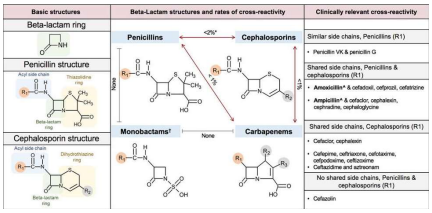
Blumenthal K et al. *Lancet*. 2019;393(10167):183-198.

Jarisch-Herxheimer Reaction

- It is a reaction to treatment and NOT AN ALLERGIC REACTION to penicillin
- Acute febrile reaction: (Headache, myalgia, chills, fever) may occur within first 24 hours after therapy
  - Release of exotoxins due to rapid lysis of organisms
  - Most common in early syphilis
  - No proven methods can prevent this reaction
  - May induce early labor/cause fetal distress
  - Symptomatic relief with antipyretics

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-#4): 39-59

Beta-lactams cross-reactivity



*Except for shared group aminopenicillins and cephalosporins.

Blumenthal K et al. *Lancet*. 2019;393(10167):183-198.

Beta-lactams cross-reactivity

Cephalosporins		Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Oxacillin	Piperacillin	Ticarcillin
1st	Cefadroxil	0.371	0.220	0.618	1.000	0.179	0.060	0.333
	Cephalexin	0.590	0.333	0.618	0.618	0.208	0.043	0.371
	Cefazolin	0.176	0.110	0.099	0.088	0.078	0.032	0.088
	Cefradine	0.344	0.200	0.117	0.371	0.155	0.092	0.263
	Cephalothin	0.583	0.371	0.117	0.295	0.154	0.035	0.208
	Cefatrizine	0.371	0.220	0.618	0.295	0.179	0.060	0.333
	Cephalexidine	0.583	0.371	0.117	0.295	0.154	0.035	0.208
2nd	Cefaclor	0.592	0.333	1.000	0.618	0.208	0.043	0.371
	Cefoxitin	0.330	0.245	0.211	0.180	0.148	0.043	0.180
	Cefprozil	0.371	0.220	0.618	1.000	0.179	0.060	0.333
	Cefuroxime	0.304	0.220	0.274	0.248	0.370	0.044	0.228
	Cefamandole	0.592	0.333	0.714	0.485	0.208	0.043	0.422
3rd	Cefixime	0.110	0.110	0.098	0.157	0.213	0.084	0.138
	Cefotaxime	0.141	0.090	0.138	0.142	0.249	0.049	0.182
	Ceftazidime	0.092	0.087	0.092	0.142	0.198	0.064	0.127
	Ceftriaxone	0.141	0.090	0.138	0.142	0.249	0.049	0.182
	Cefpodoxime	0.141	0.090	0.138	0.142	0.249	0.049	0.182
	Cefdinir	0.147	0.083	0.143	0.156	0.207	0.047	0.238
	Ceftibuten	0.167	0.127	0.148	0.165	0.237	0.079	0.165
4th	Cefepime	0.141	0.090	0.138	0.142	0.249	0.049	0.182

Piccard, M, et al. *J Allergy Clin Immunol Pract*, 7 (8) (2019), pp. 2722-2738

Penicillin Skin Testing

- Safe and validated method for evaluating IgE-mediated penicillin allergies
  - High negative predictive value (NPV): >95%
  - 2% to 3% false positive rate
  - Low positive predictive value
- Requires trained personnel
- Pharmacist play a vital role establishing penicillin desensitization protocols

Khan DA et al. J Allergy Clin Immunol. 2022;150(6):1333-1393.
Bland C et al. Am J Health-Syst Pharm. 2019;76(3):136-147.

Penicillin Desensitization Protocol

- Perform in the intensive care unit
- Beta-blockers should be discontinued
- Epinephrine, antihistamine, corticosteroids should be ordered
- Monitor ECG
- Recommended to use same route as required for therapeutic purposes

Castells M, Khan DA, Phillips EJ. *N Engl J Med* 2019; 381:2338-2351

Penicillin Desensitization Protocol

Table 2. Three-Bag, 12-Step Intravenous Penicillin Desensitization Protocol.*

Step	Bag	Rate	Time†	Volume Infused	Dose Administered	Cumulative Dose
		ml/hr	*min*	*ml*	*units*	
1	1	2.0	15	0.50	200.0	200.0
2	1	5.0	15	1.25	500.0	700.0
3	1	10.0	15	2.50	1,000.0	1,700.0
4	1	20.0	15	5.00	2,000.0	3,700.0
5	2	5.0	15	1.25	5,000.0	8,700.0
6	2	10.0	15	2.50	10,000.0	18,700.0
7	2	20.0	15	5.00	20,000.0	38,700.0
8	2	40.0	15	10.00	40,000.0	78,700.0
9	3	10.0	15	2.50	98,032.5	176,732.5
10	3	20.0	15	5.00	196,065.0	372,797.5
11	3	40.0	15	10.00	392,130.0	764,927.5
12	3	80.0	61.875	82.50	3,235,072.5	4,000,000.0

Castells M, Khan DA, Phillips EJ. *N Engl J Med* 2019; 381:2338-2351

- Indicated for patients at high risk for penicillin allergy
- IV desensitization: three bags with drug concentrations at dilutions of 1:100, 1:10, and 1:1 are administered in 12 steps
- Total time is approximately 3.7 hours
- Cannot miss doses once desensitized to maintain desensitized state

In patients with neurosyphilis where desensitization with penicillin is not feasible but are able to tolerate cephalosporins, what would be the most appropriate regimen?

A. Doxycycline 100 mg PO every 12 hours for 4 weeks
B. Ceftriaxone 2 G IV daily for 10-14 days
C. Azithromycin 2 G PO for 1 dose
D. Ceftazidime 2 G IV every 8 hours for 10-14 days

Follow-up CSF Exams After Treatment

- No need for follow-up LP at 6 months after the diagnosis and treatment of neurosyphilis in non-HIV patients or patients with HIV (PWH) who are on antiretroviral therapy (ART) if they improve clinically, and their serological titers are responding appropriately

  If serological titers do not respond appropriately (patient denies reinfection, and titers increase fourfold or fail to decline fourfold at 12 or 24 months, CSF examination should be considered

- However, for PWH who are not on ART, a follow-up CSF examination at 6 months after treatment for neurosyphilis is recommended.

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Key Takeaways

- Syphilis is on the rise and with it, neurosyphilis, ocular and otosyphilis.
- Neurosyphilis can occur at any stage of the disease.
- LP should be performed in the following patients:
  - Syphilis + neurologic symptoms
  - Syphilis signs or symptoms that persist or recur
  - Syphilis patients with a sustained four-fold increase in titer without concern for reinfection

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

Key Takeaways

- Normal CSF generally rules out neurosyphilis, but can be completely normal in ocular or otosyphilis
- Mainstay of treatment for ocular syphilis, otosyphilis, and, neurosyphilis, is IV penicillin
  - Alternative: Ceftriaxone 1-2 grams IM for 10-14 days
- Penicillin desensitization should be considered on patients with IgE-mediated allergic reactions to penicillin
- Pharmacist can play an important role establishing penicillin desensitization protocols

Workowski KA, et al. *MMWR Recomm Rep* 2021;70 (No. RR-44): 39-59

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IDSA Guideline Updates for Antimicrobial Resistant Gram-Negative Infections

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January 20th, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

Objectives

- Discuss the resistance mechanisms in gram-negative bacteria
- Summarize the 2023 IDSA Guidelines Updates on Treatment of Antimicrobial Resistant Gram-Negative Infections
- Evaluate current literature available to guide antimicrobial drug use for resistant gram-negative infections

2

Background

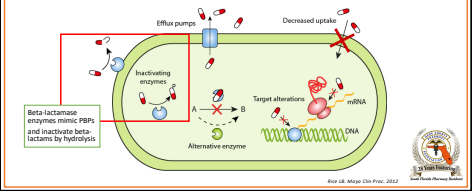
- According to the CDC Antibiotic Resistance Threats in the United States, antimicrobial resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually from 2012 through 2017
- IDSA published a guidance document focusing on infections caused by:
  - Extended-spectrum β-lactamase producing Enterobacterales (ESBL-E)
  - AmpC β-lactamase-producing Enterobacterales (AmpC-E)
  - Carbapenem-resistant Enterobacterales (CRE)
  - *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*)
  - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
  - *Stenotrophomonas maltophilia*

CDC: Centers for Disease Control and Prevention

CDC, 2019
Clin Infect Dis. 2023;ciad428.

3

General Resistance Mechanisms



Rice LB. Mayo Clin Proc. 2012

4

ampC β-lactamase Producing *Enterobacterales*

5

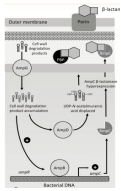
ampC Resistance

Mechanism of Resistance

- Ambler Class C
- Increased ampC production
  1. **Inducible chromosomal gene expression**
     - Occurs in presence of β-lactam and leads to production of enzyme in periplasmic space to increase MICs
     - Results in ceftriaxone, cefotaxime, and ceftazidime resistance

Common organisms

- *Enterobacter cloacae* complex
- *Klebsiella aerogenes*
- *Citrobacter freundii*



Tamma et al. 2019

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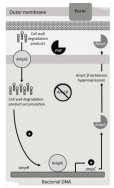
ampC Resistance

Mechanism of Resistance

- Ambler Class C
- Increased ampC production
  - **2. Stable Chromosomal Depression**
    - Leads to stable derepression of ampR resulting in over transcription of ampC, even in the absence of a β-lactam trigger
    - Due to mutations in *ampC* regulatory genes
      - ampD > ampR > ampG

Common Organisms

- *E. coli*
- *Shigella* species
- *A. baumannii*



Tamma et al. 2019

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ampC Resistance

Mechanism of Resistance

- Ambler Class C
- Increased ampC production
  - **3. Plasmid Mediated ampC**
    - Enterobacterales that do not harbor chromosomal ampC
      - *K. pneumoniae*
      - *E. coli*
      - *Salmonella*
    - Due to mutations in *ampC* regulatory genes
      - Not inducible, are continuously expressed

Tamma et al. 2019

8

ampC Diagnosis

Susceptibility Testing

- Cefoxitin resistance is used for screening of AmpC β-lactamases producers in the *Enterobacterales*
  - AmpC producers may appear susceptible to extended-spectrum cephalosporins when initially tested

Inactivation of:

- Aminopenicillins
- Cephalosporins
- Oxyimino-cephalosporins
- Cephamycins
- Aztreonam

20	Escherichia coli ac	
21		MIC (mg/
22	Amikacin	S
23	Cefepime	S
24	Cefoxitin (Urine)	R
25	Cefoxitin (Pure Urine)	R
26	Cefepime	S
27	Ceftazidime	R
28	Ceftazidime	S
29	Ceftriaxone	S
30	Gentamicin	S
31	Levofloxacin	S
32	Meropenem	S
33	Piperacillin/Tazobactam	S
34	Trimethoprim/Sulfa	S
35	Tetracycline	S
36	Tigecycline	S
37	Vibramycin	S

Clin Infect Dis. 2023;ciad428

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Agents for *ampC* Resistance

	Cefepime (Maxipime®)	Ceftriaxone (Rocephin®)	Piperacillin/Tazobactam (Zosyn®)
Recommendation	• Preferred treatment option for E. cloacae, K. aerogenes, and C. freundii infections	• Ceftriaxone is not suggested for the treatment of invasive infections caused by organisms at moderate to high risk of clinically significant ampC production (K. aerogenes, and C. freundii infections)	• Piperacillin-tazobactam is not suggested for the treatment of serious infections caused by Enterobacterales at moderate to high risk of clinically significant inducible ampC production
Rationale	• Cefepime is an oxyimino-cephalorsporin that is relatively stable against AmpC and also has low ampC induction potential • Resists hydrolysis	• Emergence of resistance after ceftriaxone exposure occurs in approximately 20% of infections caused by E. cloacae, K. aerogenes, or C. freundii	• Tazobactam is less effective at protecting β-lactams from ampC hydrolysis than newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam
Clinical Pearls	• Use caution in ampC infections with cefepime MICs of 4-8 µg/mL • Although cefepime may be effective for the treatment of ampC-E infections, it remains suboptimal against infections caused by ESBL-E	• Ceftriaxone is reasonable for uncomplicated cystitis caused by these organisms when susceptibility is demonstrated	• Piperacillin-tazobactam may be a reasonable treatment option for mild infections such as uncomplicated cystitis

MIC: Minimum Inhibitory Concentration

Clin Infect Dis. 2022;ciac628

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Cefepime for *ampC* Resistance

Design	Retrospective study
Population	305 adults with monomicrobial Enterobacter cloacae bacteremia at a medical center from 2008 to 2012
Intervention	Empiric treatment with Cefepime or Carbapenem monotherapy, administered during the first 24 hours after blood cultures had been taken
Outcome	Primary endpoint was 30-day crude mortality rate
Results	ESBL production was more common with cefepime MICs 4-8 mcg/mL (88.9% vs. 44.2%; p<0.001) vs cefepime-susceptible isolates No significant difference in mortality when using cefepime as empiric therapy (MIC ≤2). For definitive therapy, cefepime use was an independent risk factor for 30-day mortality in isolates with MIC 4-8 mcg/mL
Conclusion	Cefepime is one of the therapeutic alternatives for cefepime-susceptible *E. cloacae* bacteremia

Lee et. Al 2015

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Piperacillin-Tazobactam for *ampC* Resistance: MERINO-2 Trial

Design	International Multicenter, open-labeled, parallel-group, randomized controlled trial
Population	Adult patients with bloodstream infection due to chromosomal ampC producers
Intervention	Randomization 1:1 Piperacillin-tazobactam (4.5 grams IV every 6 hours as a standard infusion) or Meropenem (1 gram IV every 8 hours as a standard infusion) for definitive treatment of bloodstream infections caused by ampC β-lactamases
Outcome	The primary efficacy outcome was a composite of death, clinical failure, microbiological failure, and microbiological relapse at 30 days
Results	No significant differences in the primary outcome Mortality (0% versus 6%, p=0.13); clinical failure (21% versus 12%, p=0.29); microbiological failure (13% versus 0%), p=0.03), and microbiological relapse (0% versus 9%, p=0.06), for the piperacillin-tazobactam and meropenem arms, respectively
Conclusion	Among patients with bloodstream infection due to ampC producers, piperacillin-tazobactam may lead to more microbiological failures, although fewer microbiological relapses were seen

Open Forum Infect Dis. 2022

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Agents for *ampC* Resistance

	β-lactam-β-lactamase inhibitors	Cefiderocol (Fetroja®)	Non-β-lactam therapy
Recommendation	• Reserve ceftazidime-avibactam (Avycaz®), meropenem-vaborbactam (Vabomere®), and imipenem-cilastatin-relebactam (Recarbio®) for infections caused by organisms exhibiting carbapenem-resistance	• Reserve cefiderocol for infections caused by organisms exhibiting carbapenem-resistance	• Nitrofurantoin or TMP-SMX are preferred treatment options for uncomplicated AmpC-E cystitis • TMP-SMX or fluoroquinolones can be considered as step-down therapy for the treatment of invasive infections caused by organisms at moderate to high risk of AmpC production
Rationale	• Although ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam generally exhibit in vitro activity against ampC-E, higher failure rates of ampC infections compared to ESBL-E	• Cefiderocol demonstrates in vitro activity against ampC-E	• Neither TMP-SMX nor fluoroquinolones are substrates for AmpC hydrolysis
Clinical Pearls	• Ceftolozane-tazobactam should not be considered as a treatment option for AmpC-E infections (except in polymicrobial infections in which DTR- P. aeruginosa and ampC-E are isolated) • Tazobactam is not very effective in protecting β-lactams from ampC hydrolysis		• Aminoglycosides are alternative treatments for uncomplicated cystitis, pyelonephritis, and cUTI caused by AmpC-E • Nephrotoxicity risk • TMP-SMX and fluoroquinolones have good oral bioavailability

Clin Infect Dis. 2023;ciad428

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Extended-Spectrum β-lactamase Producing *Enterobacterales*

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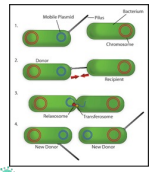
ESBL Resistance

Mechanism of Resistance
- Plasmid mediated
  - Transferable between organisms
- Ambler class A

Common organisms
- *E. coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Proteus mirabilis*

Inactivation of:
- Penicillins
- Cephalosporins
- Aztreonam



CTX-M: most common ESBL gene worldwide

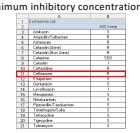
Clin Infect Dis. 2023;ciad428. Pinzol, A. 2022

15

ESBL Diagnosis

Susceptibility Testing

- Non-susceptibility to ceftriaxone
  - Ceftriaxone minimum inhibitory concentrations (MICs) ≥2 µg/mL)



- Blood Biofire CTX-M result

BC ID ESBL resistance gene-CTX-M	Not Detected	(Not Detected - 1)

Ceftazidime can also be used as a marker

Clinical and Laboratory Standards Institute 2022

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ESBL-E Treatment Recommendations

Uncomplicated Cystitis	Pyelonephritis and cUTI	Outside of the Urinary Tract
Preferred Agents	**Preferred Agents**	**Preferred Agents**
Nitrofurantoin	Trimethoprim-sulfamethoxazole	Meropenem*
Trimethoprim-sulfamethoxazole	Ciprofloxacin	Ertapenem
Alternative Agents	Levofloxacin	Imipenem-cilastatin*
Ciprofloxacin	Meropenem	**Transition Agents**
Levofloxacin	Ertapenem	Trimethoprim-sulfamethoxazole
Carbapenem	Imipenem-cilastatin	Ciprofloxacin
Single dose aminoglycosides	**Alternative Agents**	Levofloxacin
Oral fosfomycin (for *E. coli* only)	Aminoglycosides (full course)	

*For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems

Clin Infect Dis. 2013;ciad428

17

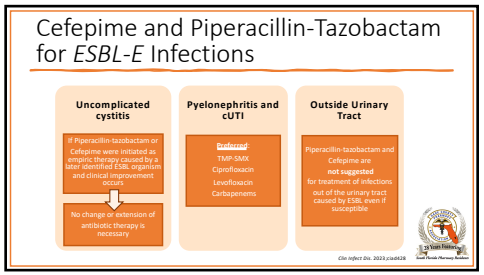
Aminoglycosides for Pyelonephritis

Design	Retrospective propensity-matched cohort study
Population	2026 patients with pyelonephritis, of which 589 patients (29%) had bloodstream infections
Intervention	715 treated with aminoglycosides and 1311 treated with non-aminoglycoside drugs (ceftriaxone, piperacillin/tazobactam, carbapenems, and fluoroquinolones)
Outcomes	The primary efficacy endpoint was all-cause mortality within 30 days of the date of the index culture
Results	Treatment with aminoglycosides was associated with a higher likelihood of in vitro activity against clinical isolates (OR = 2.0; P < 0.001) Death at 30 days occurred in 55 (7.6%) versus 145 (11%) patients treated with aminoglycosides and non-aminoglycoside drugs, respectively (adjusted HR = 0.78; P = 0.013)
Conclusion	Initial empirical treatment of pyelonephritis with aminoglycosides was associated with higher rates of in vitro activity and lower overall mortality compared with non-aminoglycoside drugs, without excess nephrotoxicity

J Antimicrob Chemother. 2020

18

Cefepime and Piperacillin-Tazobactam for *ESBL-E* Infections



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Agents Not Recommended for *ESBL-E* Infections

Cephamycins, *β*-lactam- *β*-lactamase inhibitors, and cefiderocol are **NOT** recommended for the treatment of ESBL-E infections

- Both Cefotetan and Cefoxitin are only available IV and have relatively short half-lives
- There does not appear to be an advantage with use of these agents over preferred agents for the treatment of ESBL-E infections

- *β*-lactam- *β*-lactamase inhibitors and cefiderocol exhibit activity against ESBL-E
- However, *β*-lactam- *β*-lactamase inhibitors should preferentially be reserved for treating infections caused by organisms exhibiting carbapenem-resistance
- May be considered in polymicrobial infections

Clin Infect Dis. 2023;ciad428.

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Knowledge Check

Which of the following is recommended for ESBL infections outside of the urinary tract?

a) Fosfomycin
b) Nitrofurantoin
c) Piperacillin-tazobactam
d) Meropenem

Clin Infect Dis. 2023;ciad428.

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Knowledge Check

Which of the following is recommended for ESBL infections outside of the urinary tract?

a) Fosfomycin
b) Nitrofurantoin
c) Piperacillin-tazobactam
d) **Meropenem**

Clin Infect Dis. 2023;ciad428.

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Carbapenem-Resistant *Enterobacterales*

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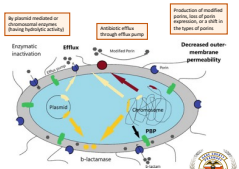
CRE Resistance

Mechanism of Resistance

- Ambler class A & B
  - Not susceptible to β-lactamase inhibitors

Common Carbapenemases

- *Klebsiella pneumoniae* Carbapenemases (KPC)
- New Delhi Metallo-β-lactamases (NDMs)
- Verona Integron-encoded Metallo-β-lactamases (VIMs)
- Imipenem-hydrolyzing Metallo-β-lactamases (IMPs)
- Oxacillinases (OXA-48-like)



Clin Infect Dis. 2023;ciad428.

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CRE Diagnosis

Susceptibility Testing

- Resistance to either meropenem or imipenem
- Resistance to at least one carbapenem other than imipenem is required for bacteria generally not susceptible to imipenem
  - Proteus spp., Morganella spp., Providencia spp.

or Enterobacterales isolates producing Carbapenemase enzymes

Carbapenemase Resistant Enterobacterales

Carbapenemase producing	Non-Carbapenemase producing
Harbor a gene encoding carbapenemase (a β-lactamase)	Result of amplification of non-carbapenemase β-lactamase genes with concurrent outer membrane porin disruption

Clin Infect Dis. 2023;ciad428

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Treatment for Non-Carbapenemases

For infections caused by Enterobacterales isolates that exhibit susceptibility to meropenem and imipenem (MICs ≤1 µg/mL), but are not susceptible to ertapenem (MICs ≥1 µg/mL)

⇨

The use of extended-infusion meropenem (or imipenem-cilastatin) is suggested, assuming no Carbapenemase has been identified

Clin Infect Dis. 2023;ciad428

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CRE Treatment Recommendations

Uncomplicated Cystitis
Preferred Agents
Nitrofurantoin
Trimethoprim-sulfamethoxazole
Ciprofloxacin
Levofloxacin
Alternative Agents
Single dose aminoglycosides
Oral fosfomycin (for *E. coli* only)
Colistin
Ceftazidime-avibactam
Meropenem-vaborbactam
Imipenem-cilastatin-relebactam
Cefiderocol

Pyelonephritis and cUTI
Preferred Agents
Trimethoprim-sulfamethoxazole
Ciprofloxacin
Levofloxacin
Ceftazidime-avibactam
Meropenem-vaborbactam
Imipenem-cilastatin-relebactam
Alternative Agents
Aminoglycosides

Outside of the Urinary Tract
Preferred Agents
When carbapenemase testing results are either not available or negative
Ceftazidime-avibactam
Meropenem-vaborbactam
Imipenem-cilastatin-relebactam
Preferred Agents
In countries with a high prevalence of metallo-β-lactam producing organisms or who have had a culture where they were identified
Ceftazidime-avibactam + aztreonam
Cefiderocol monotherapy

Clin Infect Dis. 2023;ciad428

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Cefiderocol Monotherapy: SIDERO-WT-2014 Study

Objective	Compare the activity of 8 novel B-lactams against a cohort of clinical carbapenem-resistance Enterobacterales isolates
Methods	A collection of consecutive CRE clinical isolates from unique patients at 3 US hospitals (2016–2021) Of the 603 CRE isolates, 276 (46%) were carbapenemase producing and 327 (54%) were non–carbapenemase producing. The organisms most frequently identified were *Klebsiella pneumoniae* (38%), *Enterobacter cloacae* complex (26%), and *Escherichia coli* (16%)
Results	Percent susceptibility to novel β-lactam agents: ceftazidime-avibactam (95%), meropenem-vaborbactam (92%), imipenem-relebactam (84%), and cefiderocol (92%). Cefiderocol was active against 83% of the 29 NDM-producing isolates
Conclusion	Cefiderocol is highly likely to be active against CRE clinical isolates because it exhibits activity against Enterobacterales producing any of the 5 major carbapenemase enzymes, as well as CRE isolates not producing carbapenemase

Infection Control & Hospital Epidemiology. 2023

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CRE Outside of the Urinary Tract

KPC Production

Preferred:
- Meropenem-vaborbactam
- Ceftazidime-avibactam
- Imipenem-cilastatin-relebactam

Alternatives:
- Cefiderocol

MBL Production

Preferred:
- Ceftazidime-avibactam + Aztreonam
- Cefiderocol monotherapy

OXA-48-like Production

Preferred:
- Ceftazidime-avibactam

Alternative:
- Cefiderocol

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Emergency of Resistance: *β*-lactam-*β*-lactamase Inhibitors

The emergence of resistance is a concern with all β-lactams used to treat CRE infections.
Available data suggest the frequency may be highest for ceftazidime-avibactam

Design	Retrospective single-center study
Population	37 consecutive patients treated for 3 days or longer with ceftazidime-avibactam were evaluated. Median age was 64 years. 57% were male
Intervention	A standard dose of 2.5 g intravenously (IV) every 8 hours with adjustments for renal impairment made according to manufacturer recommendations
Outcome	The primary outcome was clinical success defined as survival and absence of recurrence at 30 days following the onset of infection, resolution of signs and symptoms of infection, and sterilization of site-specific cultures within 7 days of treatment initiation
Results	Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively. In 23% (5/22) of clinical successes, CRE infections recurred within 90 days. Microbiologic failure rate was 27% (10/37). Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures
Conclusion	Resistance was detected following treatment courses of 10, 15, and 19 days

Clin Infect Dis. 2016

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Tetracycline Derivatives in *CRE*

Although β-lactam agents remain preferred treatment options for CRE infections, Tigecycline and Eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated

Tetracycline derivatives are not suggested for the treatment of CRE urinary tract infections or bloodstream infections

Clin Infect Dis. 2023;ciad428

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Not Recommended in *CRE*

Combination Therapy

The use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin is not suggested for the treatment of infections caused by CRE

Polymyxin B and Colistin

Not suggested for the treatment of infections caused by CRE.
Colistin can be considered as an alternative agent for uncomplicated CRE cystitis

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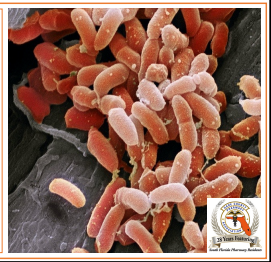
Pseudomonas aeruginosa with Difficult-to-Treat Resistance



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P. aeruginosa Resistance

Multidrug-resistant (MDR) *P. aeruginosa*	Difficult-to-Treat (DTR) *P. aeruginosa*
• *P. aeruginosa* not susceptible to at least one antibiotic in at least three antibiotics classes for which susceptibility against *P. aeruginosa* is generally expected: • Penicillins • Cephalosporins • Fluoroquinolones • Carbapenems	• *P. aeruginosa* exhibiting non-susceptibility to all of the following: • Piperacillin-tazobactam • Ceftazidime • Cefepime • Aztreonam • Meropenem • Imipenem-cilastatin • Levofloxacin • Ciprofloxacin

Clin Infect Dis. 2023;ciad428.

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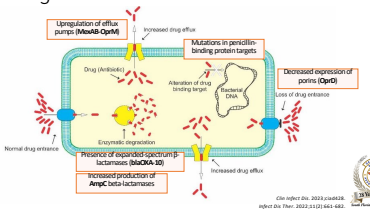
P. aeruginosa – Mechanisms of Resistance



Clin Infect Dis. 2023;ciad428.
Infect Dis Ther. 2022;11(2):661-682.

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MDR *P. aeruginosa* Recommendations

- For infections caused by carbapenem-resistant P. aeruginosa **susceptible** to traditional β-lactams:
  - Administration of a **traditional agent as high-dose extended-infusion** is suggested & repeat AST is encouraged
  - In critically ill patients or those with poor source control:
    - Use of a novel, susceptible β-lactam agent is also a reasonable treatment approach: **ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam**

AST: Antimicrobial susceptibility testing

Clin Infect Dis. 2023;ciad428.

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Traditional Anti-Pseudomonal β-Lactams

	Cefepime (Maxipime®)	Piperacillin-Tazobactam (Zosyn®)	Ceftazidime (Fortaz®)	Aztreonam (Azactam®)
Dosing	**Uncomplicated cystitis**: 1 grams IV every 8 hours, infused over 30 minutes **All other infections**: 2 grams IV every 8 hours, infused over 3 hours	4.5 grams IV every 8 hours, infused over 4 hours	2 grams IV every 8 hours, infused over 3 hours	2 grams IV every 8 hours

Clin Infect Dis. 2023;ciad428.

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Pharmacology Review of Novel BLBLIs & Cefiderocol

	Ceftolozane / Tazobactam (Zerbaxa®)	Ceftazidime / Avibactam (Avycaz®)	Imipenem / Cilastatin / Relebactam (Recarbrio®)	Cefiderocol (Fetroja®)
Dosing*	3 g IV every 8 hours	2.5 g IV every 8 hours	1.25 g IV every 6 hours	2 g IV every 8 hours†
Novel component	Ceftolozane	Avibactam	Relebactam	Cefiderocol
Additional Coverage	• MDR *P. aeruginosa*	• MDR *P. aeruginosa* • Extended-spectrum beta-lactamase (ESBL) producing gram-negative organisms • Carbapenemase-producing enterobacterales	• MDR *P. aeruginosa* • Extended-spectrum beta-lactamase (ESBL) producing gram-negative organisms • Carbapenemase-producing enterobacterales	• MDR *P. aeruginosa* • Extended-spectrum beta-lactamase (ESBL) producing gram-negative organisms • Carbapenemase-producing enterobacterales • *Acinetobacter* spp. • *Stenotrophomonas* sp.

* Renal dose adjustments required for all agents
† Augmented clearance requires an increase to 2 g IV every 6 hours

BLBLI: β-lactam-β-lactamase inhibitor

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DTR *P. aeruginosa* – General Approach

Uncomplicated Cystitis	Pyelonephritis and Complicated UTIs	Infections Outside of the Urinary Tract
Preferred Treatment	**Preferred Treatment**	**Preferred Treatment**
Ceftolozane-tazobactam	Ceftolozane-tazobactam	Ceftolozane-tazobactam
Ceftazidime-avibactam	Ceftazidime-avibactam	Ceftazidime-avibactam
Imipenem-cilastatin-relebactam	Imipenem-cilastatin-relebactam	Imipenem-cilastatin-relebactam
Cefiderocol	Cefiderocol	**Alternative Treatment**
Alternative Treatment		Cefiderocol
Tobramycin		
Amikacin		

UTI: Urinary tract infection

Clin Infect Dis. 2023;ciad428.

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DTR *P. aeruginosa* – Literature Review

Study	Design	Results	Conclusion
Pogue et al. (2020) *A retrospective, multicenter, observational cohort study*	N = 200 • MDR or XDR *P. aeruginosa* • Ceftolozane/tazobactam 1.5 – 3 g base-dose (n = 100) • Polymixin or aminoglycoside-based regimens (n = 100)	Primary cure: 81% vs. 61% (**P = 0.002**) • NNT = 5 AKI: 6% vs. 34% (**P = <0.001**) • NNH = 4 Hospital mortality: 20% vs. 25% (P = 0.40)	Favor use of ceftolozane/tazobactam over polymyxins or aminoglycosides
Stone et al. (2018) *Analysis of isolates pooled from adult Phase III clinical trials*	5 Phase III RCTs • MDR *P. aeruginosa* (n = 95) or MDR Enterobacterales (n = 101) • Ceftazidime/avibactam 2.5 g IV every 8 hours • Carbapenem comparators	Nonetheless or resistant at EOT: 17.1% vs 53.8% Clinical cure: 85.5% vs. 87.9%	Ceftazidime/avibactam is a suitable alternative to carbapenem-based therapies
RESTORE-IMI I Motsch et al. (2020) *Randomized, controlled, double-blind, phase 3 trial*	• Imipenem-nonsusceptible gram-negative infections • Imipenem/relebactam 500/250 mg every 6 hours (n = 21) • Colistin + imipenem 500 mg every 6 hours (n = 10)	Favorable overall response: 71% vs. 70% Day 28 favorable clinical response: 71% v. 40% Day 28 survival: 86% vs. 89% Nephrotoxicity: 10% vs. 31% Treatment-related: 10% vs. 56% (**P = 0.002**)	Imipenem/relebactam is an efficacious and well-tolerated treatment option for carbapenem-nonsusceptible infections.

XDR: Extensively drug-resistant
NNT: Number Needed to Treat
NNH: Number Needed to Harm

Clin Infect Dis. 2020;71(2):304-310.
J Antimicrob Chemother. 2018;73(9):2419-2424.
Clin Infect Dis. 2020;70(9):1799-1808.

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DTR *P. aeruginosa* – Metallo-β-Lactamase

- Uncommon in the United States, but more common in other regions of the world
- Resistant to all available β-lactam-β-lactamase inhibitors (BLBLIs)
  - Ceftolozane-tazobactam
  - Ceftazidime-avibactam
  - Imipenem-cilastatin-relebactam
- Preferred treatment: **cefiderocol**

Clin Infect Dis. 2023;ciad628.

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DTR *P. aeruginosa* – Literature Review

Study	Design	Results	Conclusion

CREDIBLE-CR Bassetti et al. (2021) *A randomized, open-label, multicenter, parallel-group, descriptive, phase III study*	N = 152
	• Carbapenem-resistant gram-negative infections
	• Cefiderocol 2 g IV every 8 hours (n = 101)
	  • 83% monotherapy
	• Best available therapy (n = 51)
	  • 66% colistin-based
	  • 66% combination therapy
		Clinical cure:
		• Nosocomial Pneumonia: 50% vs 53%
		• Bloodstream infection/sepsis: 43% vs. 43%
		• Complicated UTIs: 77% vs. 60%
		• Overall: 66% vs. 58%
		Microbiological eradication:
		• Complicated UTIs: 53% vs. 20%
		All-cause mortality: 34% vs. 18%
		• *Acinetobacter* spp.: 50% vs. 18%
		• *P. aeruginosa*: 18% vs. 18%
			Cefiderocol has similar clinical microbiological efficacy to best available therapy

Chou et al. (2023) *A prospective, observational descriptive study*	N = 48
	• MDR gram-negative infections
	• Cefiderocol
	  ○ Monotherapy: 31 (65%)
	  ○ Combination: 17 (35%)
	• Population
	  ○ Median age: 70.5 years
	  ○ CCI: 8.5 (6 – 11)
		Clinical failure rate: 35%
		7-day all-cause mortality: 27%
		30-day all-cause mortality: 46%
		30-day microbiologic failure: 29%
		90-day microbiologic failure: 42%
			Clinical and microbiologic failure occurred in >30% of patients treated with cefiderocol, and >40% of these died within 90 days.

CCI: Charlson comorbidity index
UTI: Urinary tract infection

Lancet Infect Dis. 2021;21(2):226-240.
Antimicrob Steward Healthc Epidemiol. 2023;3(1):e90.

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DTR *P. aeruginosa* – Combination Therapy

Combination therapy is **not** suggested if susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol has been confirmed.

If no preferred agent demonstrates activity against DTR-*P. aeruginosa*, **tobramycin** (if susceptibility is demonstrated) can be considered **in combination** with either ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or cefiderocol, preferentially selecting the β-lactam agent for which the MIC is closest to its susceptibility breakpoint

For example:

Ceftolozane-tazobactam	>128/4 mcg/mL	Highly Resistant	
Ceftazidime-avibactam	>128/4 mcg/mL	Highly Resistant	
Imipenem-cilastatin-relebactam	>4/4 mcg/mL	Intermediate Category	+ **tobramycin**

MIC: Minimum inhibitory concentration

Clin Infect Dis. 2023;ciad428.

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DTR *P. aeruginosa* – Recommendations

- The panel suggests **against** the use of nebulized antibiotics as adjunctive therapy for DTR-*P. aeruginosa* pneumonia due to:
  - The lack of benefit observed in clinical trials
  - Concerns regarding unequal distribution in infected lungs
  - Concerns for respiratory complications such as bronchoconstriction with use of aerosolized antibiotics

Clin Infect Dis. 2023;ciad428.

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Case Example

JM is a 48-year-old male admitted to the ICU for treatment of pneumonia. Cultures from a bronchial lavage reveal *P. aeruginosa* with the following susceptibilities. What is the best treatment option for this patient?

Pseudomonas aeruginosa	
	MIC Interp
Cefepime	R
Ceftazidime	R
Levofloxacin	R
Meropenem	R
Tobramycin	I
Imipenem/Relebactam	S
Cefiderocol	S
Aztreonam	R
Colistin	I
Imipenem	R
Polymyxin B	I
Ceftolozane/Tazobactam	S
Ceftazidime/Avibactam	S

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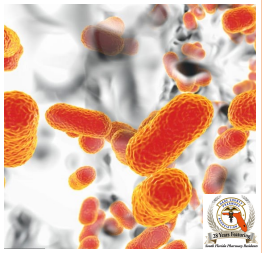
Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)



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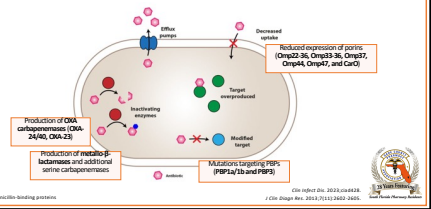
CRAB – Mechanisms of Resistance



Clin Infect Dis. 2023;ciad428.
J Clin Drugs Rev. 2013;7(11):2602-2605.

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CRAB – Management

- Management of CRAB infections is difficult for several reasons:
  1. Unclear if an isolate is a colonizing organism or true pathogen
  2. Once *A. baumannii* exhibits carbapenem resistance, it generally has acquired resistance to most other antibiotics
  3. No clear "standard of care" antibiotic regimen for CRAB infections against which to estimate the effectiveness of various treatment regimens

Clin Infect Dis. 2023;ciad428.

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CRAB – Preferred Regimen

High dose **ampicillin-sulbactam** (total daily dose of 6-9 g of the **sulbactam** component):

- Potential strategies:
  - Ampicillin-sulbactam 9 g (6 g ampicillin, 3 g sulbactam) IV every 8 hours infused over 4 hours
  - Ampicillin-sulbactam 27 g (18 g ampicillin, 9 g sulbactam) IV as a continuous infusion
  - Ampicillin-sulbactam 3 g (2 g ampicillin, 1 g sulbactam) IV every 4 hours infused over 3 hours

+

Another active agent:

- Polymyxin B
- High-dose minocycline 200 mg IV/PO every 12 hours
- High-dose tigecycline 200 mg IV x 1, then 100 mg IV every 12 hours
- Cefiderocol 2 g every 8 hours

Clin Infect Dis. 2023;ciad428.

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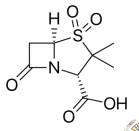
CRAB – Role of Sulbactam

- Clinically used as a β-lactamase inhibitor
- Inherent antibacterial activity against a number of bacterial species, including *Acinetobacter* spp.
- In vitro experiments have demonstrated that sulbactam binds to penicillin-binding proteins (PBPs) of *Acinetobacter* spp., which may explain the observed bacterial killing



Antimicrob Agents Chemother. 2015;59(3):1680-1689.

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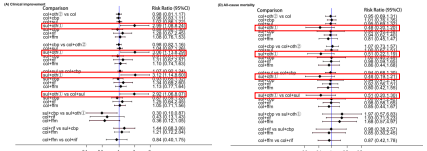
Sulbactam Therapy – Literature Review

A systemic review and network meta-analysis (Liu et al., 2021)

- High-dose sulbactam (≥6 g per day), combined with another single bacterial agent (levofloxacin or tigecycline)
- Colistin-based combination



J Glob Antimicrob Resist. 2021;24:136-147.

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CRAB – Combination Therapy vs. Monotherapy

- The panel **favors the use of combination therapy** for CRAB infections for the following reasons:
  1. Lack of robust clinical data supporting the treatment with any single agent demonstrating in vitro activity against CRAB
  2. High bacterial burdens are expected because of delays in initiating effective therapy
  3. Antibiotics that initially appear active against CRAB may rapidly develop resistance

Clin Infect Dis. 2023;ciad428.

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CRAB – Cefiderocol

- Suggested as part of a combination regimen when resistance precludes use of other agents

Study	Design	Results	Conclusion

CREDIBLE-CR Bassetti et al. (2021) *A randomized, open-label, multicenter, parallel-group, descriptive, phase III study*	N = 152
	• Carbapenem-resistant gram-negative infections
	• Cefiderocol 2 g IV every 8 hours (n = 101)
	  ▪ 83% monotherapy
	• Best available therapy (n = 51)
	  ▪ 66% colistin-based
	  ▪ 66% combination therapy
		Clinical cure:
		• Nosocomial Pneumonia: 50% vs 53%
		• Bloodstream infection/sepsis: 43% vs. 43%
		• Complicated UTIs: 77% vs. 60%
		• Overall: 68% vs. 58%
		Microbiological eradication:
		• Complicated UTIs: 53% vs. 20%
		All cause mortality: 34% vs. 18%
		• *Acinetobacter* spp.: 50% vs. 18%
		• *P. aeruginosa*: 18% vs. 18%
			Cefiderocol has similar clinical microbiological efficacy to best available therapy

UTI: Urinary tract infection

Clin Infect Dis. 2023;ciad428.

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CRAB – Recommendations

- The panel suggests **against** the use of:
  - Extended-infusion meropenem or imipenem-cilastatin
  - Rifabutin and other rifamycins
  - Nebulized antibiotics

Clin Infect Dis. 2023;ciad428.

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Knowledge Check

Which antibiotic is recommended first line to be included in combination therapy for carbapenem-resistant *Acinetobacter baumannii*?

a) Ampicillin-sulbactam
b) Ceftolozane-tazobactam
c) Ceftazidime-avibactam
d) Cefiderocol

Clin Infect Dis. 2023;ciad428.

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Knowledge Check

Which antibiotic is recommended first line to be included in combination therapy for carbapenem-resistant *Acinetobacter baumannii*?

a) Ampicillin-sulbactam
b) Ceftolozane-tazobactam
c) Ceftazidime-avibactam
d) Cefiderocol

Clin Infect Dis. 2023;ciad428.

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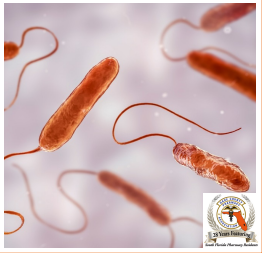
Stenotrophomonas Maltophilia



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S. Maltophilia

- Aerobic, glucose nonfermenting, gram-negative bacillus that is ubiquitous in water environments
- Believed to be less pathogenic than other organisms
- However, it produces biofilm and virulence factors that can enable colonization or infection in vulnerable hosts, such as those with underlying lung disease and hematological malignancies

Clin Infect Dis. 2023;ciad428.

58

S. Maltophilia – Management

- Management of *S. maltophilia* infections is difficult for several reasons:
  1. Unclear is an isolate is a colonizing organism or true pathogen
  2. Number of antimicrobial resistance genes and gene mutations carried by *S. maltophilia* isolates
  3. No clear "standard of care" antibiotic regimen for *S. maltophilia* infections against which to estimate the effectiveness of various treatment regimens
  4. Susceptibility testing determination is problematic, with only 5 agents with interpretable antibiotic MIC data

MIC: Minimum inhibitory concentration

Clin Infect Dis. 2023;ciad428.

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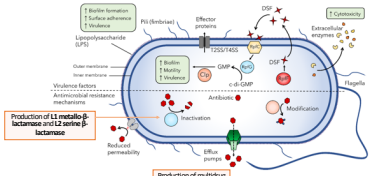
S. Maltophilia – Mechanisms of Resistance



Viruses. 2021;13(6):1057.

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S. Maltophilia – General Approach to Treatment

Preferred Regimens

Combination therapy with two of the following agents:

Trimethoprim-sulfamethoxazole
Minocycline or Tigecycline
Levofloxacin
Cefiderocol

When significant clinical instability is evident or intolerance to or inactivity of other agents is identified:

Ceftazidime-avibactam
+
Aztreonam

Clin Infect Dis. 2022;ciac826.

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S. Maltophilia – TMP-SMX Dosing

- A study in pediatric patients comparing two dosing regimens of TMP-SMX:
  - **Lower dose**: 4 – 7 TMP mg/kg/day
  - **Higher dose**: 20 TMP mg/kg/day
  - Mortality rates were higher in the lower doses than in the higher doses (33% vs. 14%)
  - TMP-SMX dosing recommendation of 15-20 mg/kg/day was extrapolated from pediatric patients with hematological malignancies based on this study
- PK study evaluated TMP serum concentrations in pediatric patients vs. in adult patients
  - Showed that lower doses of TMP (12.5 mg/kg/day) were needed in adults to achieve the same target TMP concentration

TMP-SMX: Trimethoprim-sulfamethoxazole
PK: Pharmacokinetic

Can Med Assoc J. 1975;112(13 Spec No):47-50.
Rev Infect Dis. 1982;4(2):464-478.

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S. Maltophilia – TMP-SMX Dosing

Study	Design	Results	Conclusion
Czosnowski et al. (2011) *A retrospective study*	N = 101 patients with VAP • TMP-SMX 11.2 mg/kg/day (n = 77) • Ciprofloxacin (n = 14)	Overall clinical success: 87% Microbiologic plus clinical success: 82%	The use of TMP-SMX or ciprofloxacin resulted in high cure rates
Nys et al. (2019) *A retrospective, single-center study*	N = 76 • TMP-SMX 10.3 mg/kg/day (n = 45) • Levofloxacin 500 mg/day (n = 31)	Overall clinical cure: 79% Microbiological eradication: 82% 28-day mortality: 14%	The use of TMP-SMX or levofloxacin resulted in high cure rates

The panel suggests a dose range of **8-12 mg/kg** (trimethoprim component) of TMP/SMX

TMP-SMX: Trimethoprim-sulfamethoxazole
VAP: Ventilator-associated pneumonia

Pharmacotherapy. 2011;31(4):338-345.
Antimicrob Agents Chemother. 2019;63(11):e00784-19.

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Knowledge Check

Which antibiotic is NOT recommended as part of a treatment regimen for *S. maltophilia*?

a) TMP-SMX
b) Minocycline
c) Cefiderocol
d) Tobramycin

Clin Infect Dis. 2023;ciad428.

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Knowledge Check

Which antibiotic is NOT recommended as part of a treatment regimen for *S. maltophilia*?

a) TMP-SMX
b) Minocycline
c) Cefiderocol
d) Tobramycin

Clin Infect Dis. 2023;ciad428.

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IDSA Guideline Updates for Antimicrobial Resistant Gram-Negative Infections

Valerie Hernandez & **Emily Perez**
Jackson Memorial Hospital
Miami, FL

January 20th, 2024

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