# Welcome to the NDSHP 2023

# Therapeutic Debates and Public Speaking for Pharmacists

SAIDEE OBERLANDER, PHARMD, BCPS

ACUTE CARE PHARMACIST – ESSENTIA HEALTH FARGO

PRESIDENT-ELECT NDSHP

# Disclosure

Saidee Oberlander, PharmD, BCPS has no relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

At the completion of this activity, the participant will be able to:

1. Define the purpose and nature of a therapeutic debate.

2. Explain the role for debate in medical education.

3. Discuss approaches to designing and presenting a therapeutic debate.

4. Review general public speaking principals applicable to pharmacists.


# What is a Debate?

11,001 Angry Politician Stock Photos, High-Res Pictures, and Images - Getty Images [Internet]. [cited 2023 Oct 16]. Available from: https://www.gettyimages.com/photos/angry-politician
470+ Student Debate Illustrations, Royalty-Free Vector Graphics & Clip Art - iStock | Student debate team, College student debate, Student debate podium [Internet]. [cited 2023 Oct 16]. Available from: https://www.istockphoto.com/illustrations/student-debate
Poll: Who won the Louisiana Governor's debate? [Internet]. [cited 2023 Oct 16]. Available from: https://www.klfy.com/your-local-election-hq/poll-who-won-the-louisiana-governors-debate/

# What is a Debate?

Organized argument discussing an idea from two or more opposing viewpoints

Use evidence to support ideas

Argument and Argumentation > Historical Supplement: Argumentation in the history of philosophy (Stanford Encyclopedia of Philosophy) [Internet]. [cited 2023 Oct 16]. Available from: https://plato.stanford.edu/entries/argument/supplement.html
American Debate League [Internet]. [cited 2023 Oct 16]. What is Debate? Available from: https://www.americandebateleague.org/what-is-debate.html

# What is a Therapeutic Debate?

Debate of controversial topic in medicine

Comparison of therapy approaches

No clear expert consensus

Help guide audience through multiple sides of an issue

### Adult Learning Theory

Self-directed, take responsibility

Learn best when see need and immediate relevance of content, clear focus, learning is experiential

### Self-Determination Theory

Encourages engagement and motivation

Active listening of alternative viewpoints

### Social Learning Theory

Learning is a social process

Must have trust, respect, and honesty for debate to be useful

# Why Therapeutic Debate?

Omelicheva MY, Avdeyeva O. Teaching with Lecture or Debate? Testing the Effectiveness of Traditional versus Active Learning Methods of Instruction. APSC. 2008 Jul;41(3):603–7

# Why Therapeutic Debate?

- Evidence-based learning
- Content-reinforcement
- Promotes active listening
- Formulate arguments
- Variety increases attention

| Speech | Abbreviation | Time Limit |
|---|---|---|
| 1st Affirmative Constructive | 1AC | 8 minutes |
| Negative Cross-Examination of Affirmative | | 3 minutes |
| 1st Negative Constructive | 1NC | 8 minutes |
| Affirmative Cross-Examination of Negative | | 3 minutes |
| 2nd Affirmative Constructive | 2AC | 8 minutes |
| Negative Cross-Examination of Affirmative | | 3 minutes |
| 2nd Negative Constructive | 2NC | 8 minutes |
| Affirmative Cross-Examination of Negative | | 3 minutes |
| 1st Negative Rebuttal | 1NR | 5 minutes |
| 1st Affirmative Rebuttal | 1AR | 5 minutes |
| 2nd Negative Rebuttal | 2NR | 5 minutes |
| 2nd Affirmative Rebuttal | 2AR | 5 minutes |
| Prep Time (each team) | | 8 minutes |

| Speech | Time Limit | Purpose |
|---|---|---|
| Team A Speaker 1 – Constructive | 4 minutes | Present the team's case |
| Team B Speaker 1 – Constructive | 4 minutes | Present the team's case |
| Crossfire | 3 minutes | Speaker 1 from Team A & B alternate asking and answering questions |
| Team A Speaker 2 – Rebuttal | 4 minutes | Refute the opposing side's arguments |
| Team B Speaker 2 – Rebuttal | 4 minutes | Refute the opposing side's arguments |
| Crossfire | 3 minutes | Speaker 2 from Team A & B alternate asking and answering questions |
| Team A Speaker 1 – Summary | 3 minutes | Begin crystallizing the main issues in the round |
| Team B Speaker 1 – Summary | 3 minutes | Begin crystallizing the main issues in the round |
| Grand Crossfire | 3 minutes | All four debaters involved in a crossfire at once |
| Team A Speaker 2 – Final Focus | 2 minutes | Explain reasons that you win the round |
| Team B Speaker 2 – Final Focus | 2 minutes | Explain reasons that you win the round |

# Debate Formats

Competition Events [Internet]. National Speech & Debate Association. [cited 2023 Oct 16]. Available from:

# Lincoln-Douglas Debate

| Speech | Time Limit | Purpose |
|---|---|---|
| Affirmative Constructive | 6 minutes | Present the affirmative case |
| Negative Cross-Examination | 3 minutes | Negative asks questions of the affirmative |
| Negative Constructive | 7 minutes | Present the negative case and refute the affirmative case |
| Affirmative Cross-Examination | 3 minutes | Affirmative asks questions of the negative |
| First Affirmative Rebuttal | 4 minutes | Refute the negative case and rebuild the affirmative case |
| Negative Rebuttal | 6 minutes | Refute the affirmative case, rebuild the negative case, and offer reasons that negative should win the round, commonly referred to as voting issues. |
| 2nd Affirmative Rebuttal | 3 minutes | Address negative voting issues and offer reasons for why the affirmative should win. |

Lincoln-Douglas debates | Summary, Dates, Significance, & Facts | Britannica [Internet]. [cited 2023 Oct 16]. Available from: https://www.britannica.com/event/Lincoln-Douglas-debates
Josh Roberts. Lincoln-Douglas Debate: an Introduction [Internet]. National Forensic League; 2012 [cited 2023 Oct 16]. Available from: https://www.speechanddebate.org/wp-content/uploads/Intro_to_LD.J.Roberts.7.5.27.pdf

# Modified Lincoln-Douglas

| |
|---|
| Introduction |
| Pro – 10-15 minutes |
| Con – 10-15 minutes |
| Pro Rebuttal – 5-10 minutes |
| Con Rebuttal – 5-10 minutes |
| *Optional 2nd Pro rebuttal – 5-8 minutes |
| *Optional 2nd Con rebuttal – 5-8 minutes |
| Conclusion |

# Preparing the Presentation

Select Topic

Clarify scope

Literature review

- Literature that supports your position
- Literature that does NOT support your position

Collaborate with partner

# Modified Lincoln-Douglas

| |
|---|
| Introduction |
| Pro – 10-15 minutes |
| Con – 10-15 minutes |
| Pro Rebuttal – 5-10 minutes |
| Con Rebuttal – 5-10 minutes |
| *Optional 2nd Pro rebuttal – 5-8 minutes |
| *Optional 2nd Con rebuttal – 5-8 minutes |
| Conclusion |

# Slide Design

- Limit number of words on slide
- Limit punctuation
- Ensure readability
- Visual variety (but not too busy)
- Make it purposeful
- Limit transitions and animations
- Minimize slide number

Tips for Making Effective PowerPoint Presentations [Internet]. [cited 2023 Oct 16]. Available from: https://www.ncsl.org/legislative-staff/lscc/tips-for-making-effective-powerpoint-presentations

Do not just read from slide

Face the audience

Stand if you can

Practice with your technology (if possible)

“Play” with your partner

# Presenting the Debate

# Public Speaking Principals

1. Practice, practice, practice
2. Avoid filler words
3. Ensure clear transitions
4. Use movement, but make it purposeful
5. Make eye contact with your audience
6. Project to the back of the room

Professional Development | Harvard DCE [Internet]. 2020 [cited 2023 Oct 16]. 10 Tips for Improving Your Public Speaking Skills. Available from: https://professional.dce.harvard.edu/blog/10-tips-for-improving-your-public-speaking-skills/
How to Speak in Public - The New York Times [Internet]. [cited 2023 Oct 16]. Available from: https://www.nytimes.com/article/how-to-speak-in-public.html

# Have Fun!


- SAIDEE OBERLANDER, PHARMD, BCPS
- SAIDEE.OBERLANDER@ESSENTIAHEALTH.ORG

# Which of the following best describes a therapeutic debate?

A. A lecture given by one presenter of a controversial topic in medicine

B. An unstructured debate between two presenters with no preparation

C. A lecture with two presenters of a well-defined topic in medicine

D. A simulated debate presentation by two or more presenters of a controversial topic in medicine

# Which of the following is true of public speaking?

A. Being conscious and purposeful with images, transitions, and movement will maximize their impact

B. It is not necessary to practice a presentation before presenting if you are familiar with the material

C. Slides should contain as much information as possible to ensure the message is passed on to the audience

D. Eye-contact and non-verbal communication are not important when presenting virtually

# References


1. Professional Development | Harvard DCE [Internet]. 2020 [cited 2023 Oct 16]. 10 Tips for Improving Your Public Speaking Skills. Available from: https://professional.dce.harvard.edu/blog/10-tips-for-improving-your-public-speaking-skills/
2. A novel learning experience: case-based, evidence-based debate - Ong - 2010 - Medical Education - Wiley Online Library [Internet]. [cited 2023 Oct 16]. Available from: https://asmepublications.onlinelibrary.wiley.com/doi/10.1111/j.1365-2923.2010.03644.x
3. Argument and Argumentation > Historical Supplement: Argumentation in the history of philosophy (Stanford Encyclopedia of Philosophy) [Internet]. [cited 2023 Oct 16]. Available from: https://plato.stanford.edu/entries/argument/supplement.html
4. mrsstrickey. Teach With Mrs T. 2020 [cited 2023 Oct 16]. Bloom's Taxonomy. Available from: https://www.teachwithmrst.com/post/bloom-s-taxonomy
5. Competition Events [Internet]. National Speech & Debate Association. [cited 2023 Oct 16]. Available from: https://www.speechanddebate.org/competition-events/
6. How to Speak in Public - The New York Times [Internet]. [cited 2023 Oct 16]. Available from: https://www.nytimes.com/article/how-to-speak-in-public.html
7. Ang RX, Chew QH, Sum MY, Sengupta S, Sim K. Systematic review of the use of debates in health professions education – does it work? GMS J Med Educ. 2019 Aug 15;36(4):Doc37.
8. Omelicheva MY, Avdeyeva O. Teaching with Lecture or Debate? Testing the Effectiveness of Traditional versus Active Learning Methods of Instruction. APSC. 2008 Jul;41(3):603–7.
9. Tips for Making Effective PowerPoint Presentations [Internet]. [cited 2023 Oct 16]. Available from: https://www.ncsl.org/legislative-staff/lscc/tips-for-making-effective-powerpoint-presentations
10. American Debate League [Internet]. [cited 2023 Oct 16]. What is Debate? Available from: https://www.americandebateleague.org/what-is-debate.html
11. Lincoln-Douglas debates | Summary, Dates, Significance, & Facts | Britannica [Internet]. [cited 2023 Oct 16]. Available from: https://www.britannica.com/event/Lincoln-Douglas-debates
12. Josh Roberts. Lincoln-Douglas Debate: an Introduction [Internet]. National Forensic League; 2012 [cited 2023 Oct 16]. Available from: https://www.speechanddebate.org/wp-content/uploads/Intro_to_LD.J.Roberts.7.5.27.pdf

# CPE Instructions for:

## Therapeutic Debates and Public Speaking for Pharmacists

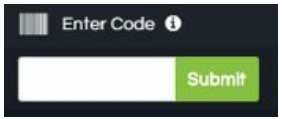
**1**

Redeem your credit online at **CEimpact.com**

*If this is the first time you have utilized the CEimpact Learning Management System (LMS) you will need to create an account.

**2**

From the **CEimpact.com** Homepage – enter the code provided in the 'Enter Code' box and click SUBMIT.




**3**

Complete the Exam & Evaluation as prompted; click SUBMIT to send your information to CPE Monitor. Follow instructions to access your CPE Statement of Credit on CPE Monitor or access your Certificate of Completion in MyCourses.

# Pharmacist Code: 9tAanr

**The deadline for obtaining your CPE Credit is 30 days from today.** The deadline is non-negotiable due to CPE Monitor reporting policies. For CME, access your certificate of completion in My Courses for this course.

# EXPANDING ANTIMICROBIAL STEWARDSHIP IN NORTH DAKOTA

Emily Perry, Pharm D

Antimicrobial Stewardship Lead

NDSU Center for Collaboration and Advancement in Pharmacy

# Disclosure

- Support for all or part of these activities has been provided by the Department of Health and Human Services through the CDC Epidemiology and Laboratory Capacity program.
- Emily Perry does not have any relevant financial relationships for this presentation to disclose.

# Learning Objectives

At the competition of this activity, participants will be able to:

- Describe how North Dakota is expanding antimicrobial stewardship (AS).
- Discuss current statewide projects.
- Recall the Core Elements of Antimicrobial Stewardship for Health Departments and the priority elements for hospital stewardship programs.
- Outline ways facilities and pharmacists can get involved in stewardship.

# Pre-assessment Question

- True or False: Education is one the core elements of antimicrobial stewardship for hospitals, but it is NOT a priority element?

- North Dakota's Department of Health and Human Services are meeting the Core Elements of Antimicrobial Stewardship for Health Departments by doing which of the following:
  A. Using National Healthcare Safety Data to track hospitals Core Element uptake
  B. Providing education sessions and webinars to healthcare professionals
  C. Creating the North Dakota Antimicrobial Stewardship Honor Roll to highlight stewardship activities in the state.
  D. All the above

# Antimicrobial Stewardship

- Required by The Joint Commission (JC) and the Center for Medicare and Medicaid Services (CMS) for all hospitals and long-term care facilities
  - JC 8 Elements of Performance
  - CMS Participation Rules

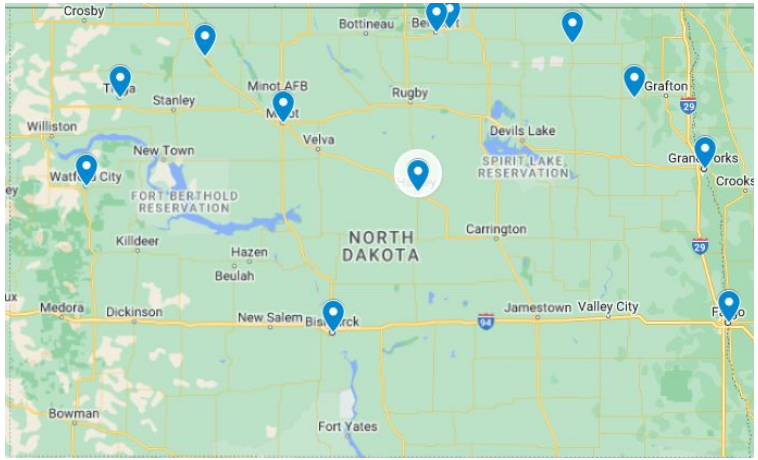
# Core Elements of Antimicrobial Stewardship for Health Departments


https://www.cdc.gov/antibiotic-use/core-elements/health-departments.html

NDSU CENTER FOR COLLABORATION AND ADVANCEMENT IN PHARMACY

# North Dakota Expanding Stewardship

- Collaborating with North Dakota's Department of Health and Human Services Division of Public Health (HAI/AR team)
  - Strengthen current antimicrobial practices
  - Initiate new programs to address stewardship
- Engage with facilities to meet CDC's seven core elements of antimicrobial stewardship
  - Survey to long-term care facilities
  - National Healthcare Safety Network (NHSN) annual survey (hospitals)



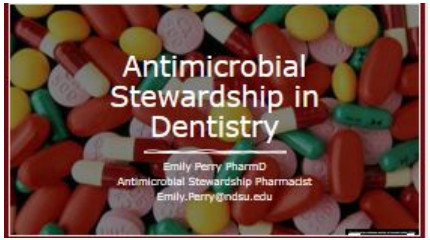

https://www.maps-of-the-usa.com/usa/north-dakota/large-detailed-roads-and-highways-map-of-north-dakota-state-with-all-cities

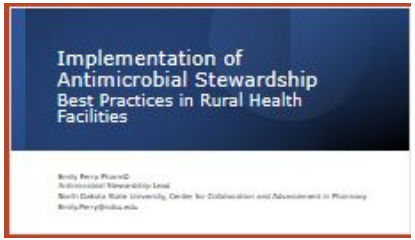
# North Dakota Expanding Stewardship

- Track antibiotic prescribing data
  - North Dakota Medicaid
  - Working to get outpatient antibiotic prescription data from national database
- Collaborate with partners
  - Quality Improvement Organization (QIO)
  - ND Quality Health Associates (QHA)
  - Center for Rural Health

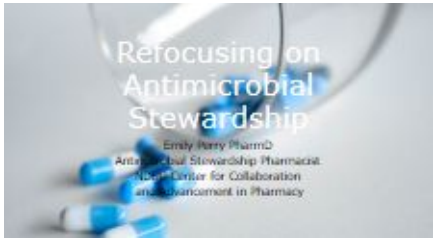
# North Dakota Expanding Stewardship

- Educate and promote antimicrobial stewardship

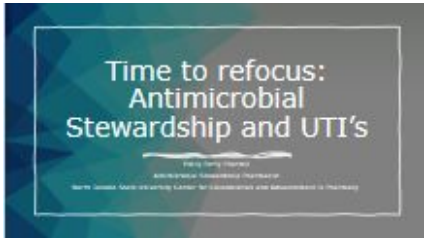










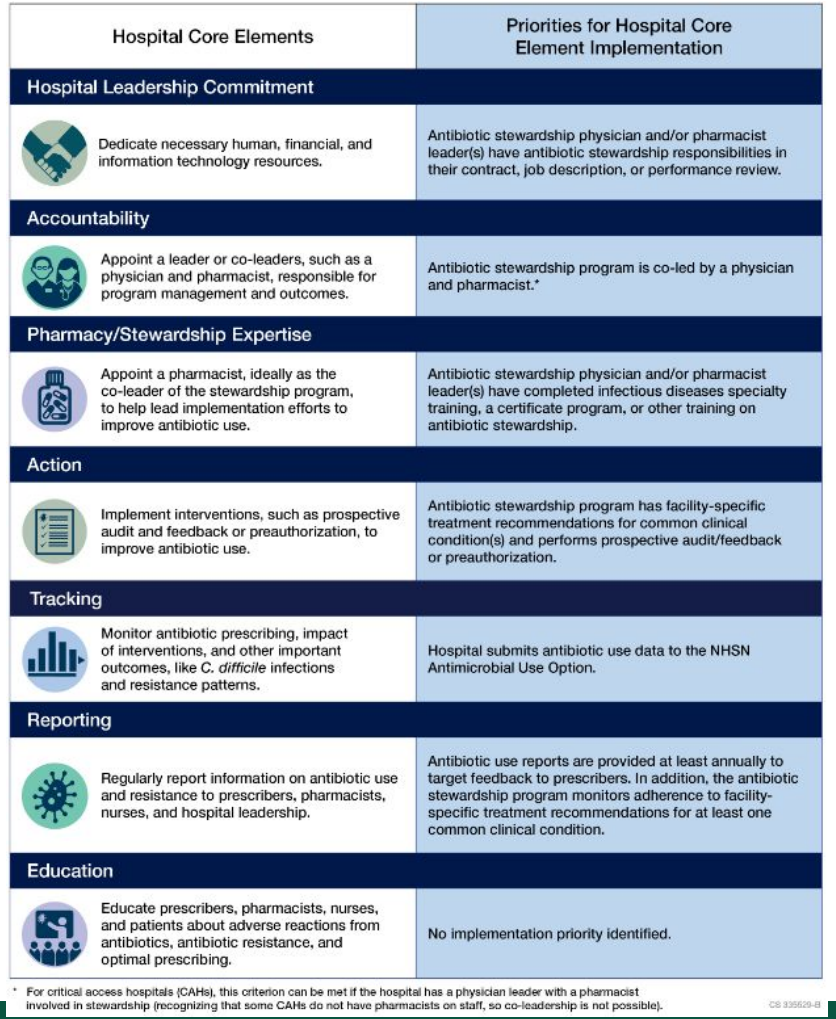

NDSU | CENTER FOR COLLABORATION AND ADVANCEMENT IN PHARMACY

# Why is expanding stewardship important?

- Only 20% of eligible hospitals are currently reporting AU/AR data to NHSN
- In 2021, 6 out of 46 hospitals in ND self-reported not meeting all 7 Core Elements of AS.
  - In 2022, there was 4 not meeting all core elements
- In 2021 no hospitals were meeting the CDC's Priority elements for AS!
  - In 2022, there are 2 hospitals meeting all 6 priority elements

Stats are from NHSN's Annual Hospital Survey

# CDC's Priority Elements



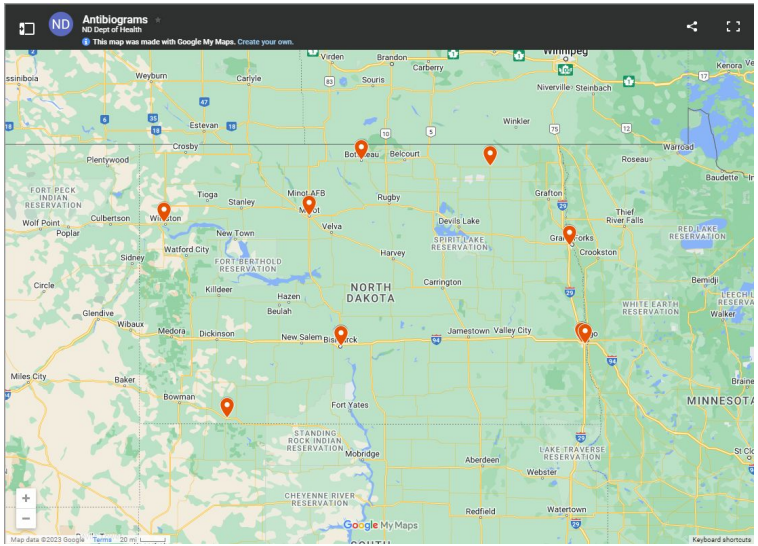
| Hospital Core Elements | Priorities for Hospital Core Element Implementation |
|---|---|
| **Hospital Leadership Commitment** | |
| Dedicate necessary human, financial, and information technology resources. | Antibiotic stewardship physician and/or pharmacist leader(s) have antibiotic stewardship responsibilities in their contract, job description, or performance review. |
| **Accountability** | |
| Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes. | Antibiotic stewardship program is co-led by a physician and pharmacist.* |
| **Pharmacy/Stewardship Expertise** | |
| Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use. | Antibiotic stewardship physician and/or pharmacist leader(s) have completed infectious diseases specialty training, a certificate program, or other training on antibiotic stewardship. |
| **Action** | |
| Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use. | Antibiotic stewardship program has facility-specific treatment recommendations for common clinical condition(s) and performs prospective audit/feedback or preauthorization. |
| **Tracking** | |
| Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns. | Hospital submits antibiotic use data to the NHSN Antimicrobial Use Option. |
| **Reporting** | |
| Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership. | Antibiotic use reports are provided at least annually to target feedback to prescribers. In addition, the antibiotic stewardship program monitors adherence to facility-specific treatment recommendations for at least one common clinical condition. |
| **Education** | |
| Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing. | No implementation priority identified. |

* For critical access hospitals (CAHs), this criterion can be met if the hospital has a physician leader with a pharmacist involved in stewardship (recognizing that some CAHs do not have pharmacists on staff, so co-leadership is not possible).

CS 335629-B

https://www.cdc.gov/antibiotic-use/images/CoreElements-Hospital-Priorities-Table.jpg

# 2023 State-wide Projects

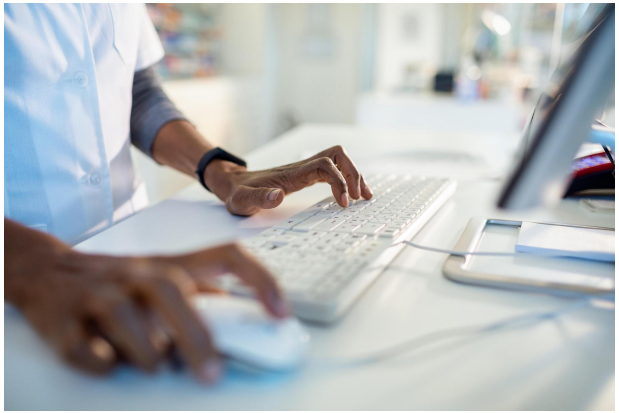



- Antibiogram website
  - North Dakota Health and Human Services webpage
  - https://www.hhs.nd.gov/health/diseases-conditions-and-immunization/antibiotic-resistance-and-antimicrobial-stewardship/antibiotic-resistance-and-antimicrobial-stewardship/antibiograms
  - Great reference for facilities with lower volumes of cultures that are unable to create an antibiogram
  - Can use to look for regional resistance patterns
  - THANK YOU to the sites that have shared their antibiograms!

Always looking to add more sites!!!

NDSU CENTER FOR COLLABORATION AND ADVANCEMENT IN PHARMACY

# 2023 State-wide Projects



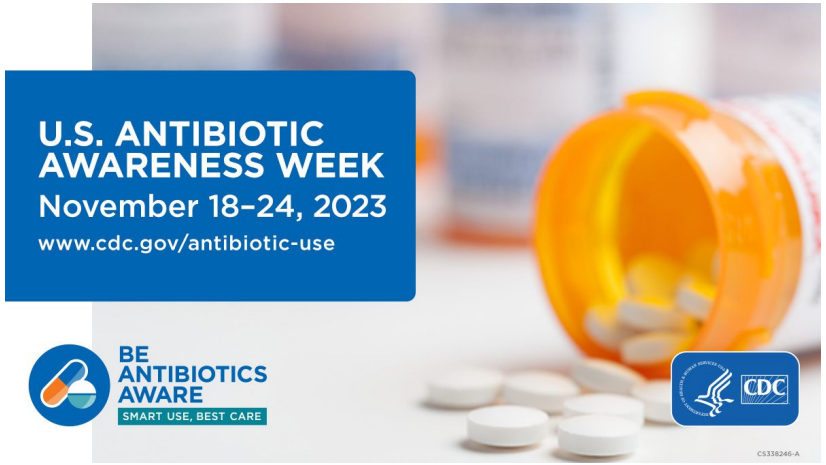
## SIDP Antimicrobial Stewardship Certificate

- Program in its 5th year
- Enrolled 104 pharmacists in North Dakota
  - 18 just began program in August 2023
  - 32 have completed the program
  - 52 are at various stages within the program
  - 2 withdrew
- Program has three phases
  - Phase one: Online modules
  - Phase two: Live webinars
  - Phase three: Implement a stewardship initiative in a healthcare facility

Data collected by NDSU's CAP Center

# 2023 State-wide Projects

- Highlighting SIDP projects in North Dakota
  - Guideline and order set builds for hospitals and outpatient clinics
  - Pre-op antibiotic auto-substitution policy
  - UTI duration policy
  - Sepsis antibiotic notes to physicians built in EMR
  - So many more impactful interventions!!!



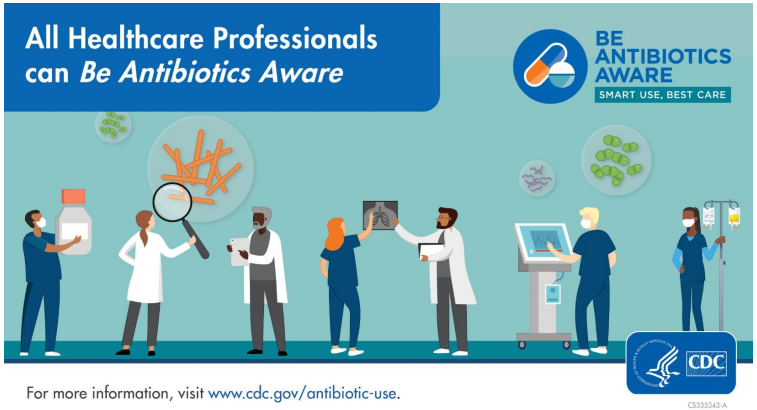
# 2023 State-wide Projects

- Antimicrobial Stewardship Honor Roll
  - Open to hospital and long-term care facilities
  - Information and applications available online
  - https://www.hhs.nd.gov/health/diseases-conditions-and-immunization/antibiotic-resistance-and-antimicrobial-stewardship/honor-roll
  - Applications due October 31st


NDSU CENTER FOR COLLABORATION AND ADVANCEMENT IN PHARMACY

# 2023 State-wide Projects

- Antibiotic Answers
  - Short 3-5 minute video's
  - Posted on the CAP Center's YouTube channel
  - Highlight antibiotic questions for different disease states, updated guidelines, and questions from healthcare professionals on antibiotics
  - Feel free to send questions to Emily.perry@ndsu.edu



# Other 2023 projects

- Working with IHS to create study on ceftriaxone use in a clinic
- Created an antimicrobial stewardship committee at a CAH
- Working on providing physician report cards to an ambulatory clinic
- Provided education on AS to physicians at two CAH
- Provided lots of resources to long-term care facilities and critical access hospitals and guidance on policy creation
- Being the antimicrobial stewardship expert for sites in North Dakota

# Future Projects

- Create a statewide antimicrobial stewardship support group
  - Infectious disease physicians and pharmacists
  - Share ideas for stewardship, projects, and new guidelines/ID info
- Host antimicrobial stewardship course
  - Ambulatory clinics
  - Review core elements and design a project to implement in the clinic
- Develop training material for medical and pharmacy students

NDSU | CENTER FOR COLLABORATION AND ADVANCEMENT IN PHARMACY

# How to get involved

- Share antibiogram with NDHHS!
- Apply for North Dakota's Antimicrobial Stewardship Honor Roll
- Email Emily.perry@ndsu.edu if your site isn't meeting the CDC's Core Elements of Antimicrobial Stewardship or if you want to expand your stewardship program
- Work with Infection Preventionist to complete the Annual Survey
- **GO PURPLE** for U.S. Antibiotic Awareness Week Nov 18-24th
  - Wear **purple** and post pictures on social media tagging #USAAW23 or #GoPurpleForAR

# U.S. Antibiotic Awareness Week

- An opportunity to highlight the importance of improving antibiotic and antifungal use, raise awareness of antimicrobial resistance, and how we can combat this global threat
- Fun events Nov 14-28
  - Go Purple for USAAW
  - Social Media chats
  - Podcasts
  - Free webinars

# CDC's Resources

- Antibiotic Stewardship resource bundles
  https://www.cdc.gov/antibiotic-use/week/toolkit/handouts.html
  - Outpatient Care
  - Dental Care
  - Long-term Care
  - Acute Care
  - Transitions of Care

# Discussion Question #1

- What statewide initiatives around antimicrobial stewardship would you like to see?

# Discussion question #2

What type of support does your antimicrobial stewardship program need?

- Physician education?
- Stewardship training?
- Stewardship technology?

# Post Assessment Questions

- The following are priority core elements of antibiotic stewardship for hospitals except:
  A. Leadership Commitment
  B. Action
  C. Education
  D. Tracking
- North Dakota's Health and Human Services are meeting which of the following core elements of antibiotic stewardship for health departments
  A. Education
  B. Leadership commitment
  C. Action
  D. B and C only
  E. A, B, and C

# Thank you for all the Antimicrobial Stewardship work you do!

Emily Perry PharmD

Antimicrobial Stewardship Lead

Email: Emily.Perry@ndsu.edu

# CPE Instructions for:

## Expanding Antimicrobial Stewardship in North Dakota

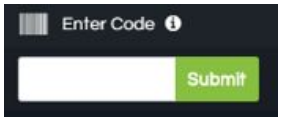
**1**

Redeem your credit online at **CEimpact.com**

*If this is the first time you have utilized the CEimpact Learning Management System (LMS) you will need to create an account.

**2**

From the **CEimpact.com** Homepage – enter the code provided in the 'Enter Code' box and click SUBMIT.




**3**

Complete the Exam & Evaluation as prompted; click SUBMIT to send your information to CPE Monitor. Follow instructions to access your CPE Statement of Credit on CPE Monitor or access your Certificate of Completion in MyCourses.

# Pharmacist Code: IPf9nA

**The deadline for obtaining your CPE Credit is 30 days from today.** The deadline is non-negotiable due to CPE Monitor reporting policies. For CME, access your certificate of completion in My Courses for this course.

# Ketamine:
# To the ED and Beyond!

THE KETLAR PRIMER

LARISSA OSTFELD, PHARMD
ESSENTIA HEALTH

# Disclaimer

- The presenter has no financial relationships with ineligible companies, relevant to this presentation to disclose.
- This presentation will discuss off label uses of medications

# Learning Objectives

*At the completion of this activity, the participant will be able to:*

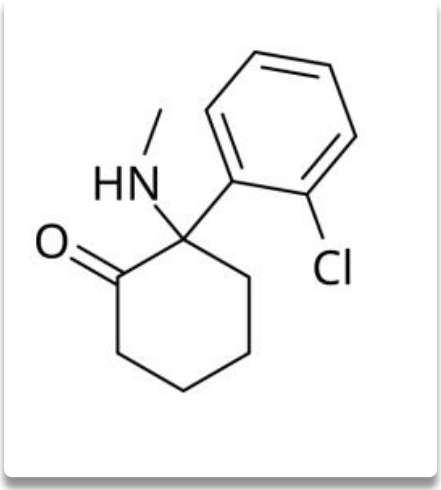
- *1. Summarize what is known about ketamine for depression.*
- *2. List the different dosing strategies for ketamine by indication.*
- *3. Discuss indications and uses for ketamine.*
- *4. Describe ketamine's proposed mechanism of action.*

# What is Ketamine?

PCP derivative racemic compound

Receptors:

- **NMDA noncompetitive antagonist**
- Inhibition of GABAergic interneuron
- Partial mu opioid agonist
- NMDAR (glutamate) antagonist




Rosenbaum et al. NIH (2022) StatPearls Ketamine Image: Wikipedia Ketamine

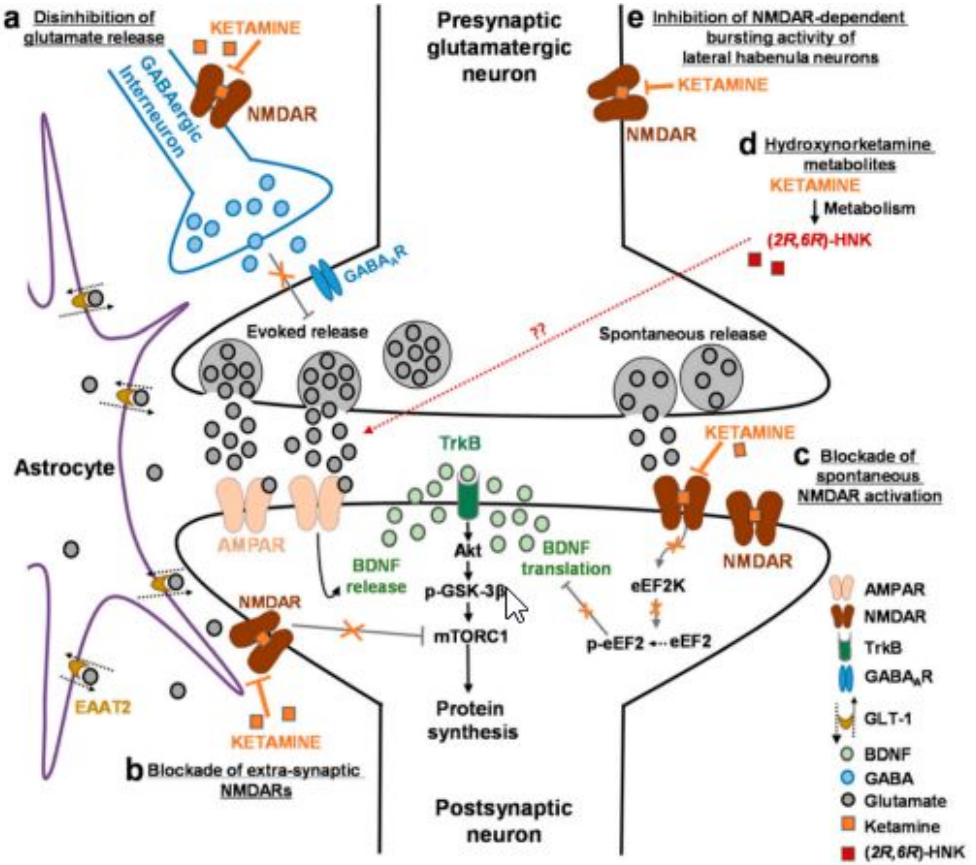



Image: https://tinyurl.com/mr3rcz3y

# What is Ketamine Used For?

FDA approved: anesthesia and procedural sedation

Off-label indications: pain, depression, agitation, seizures

Rosenbaum et al. NIH (2022) StatPearls Ketamine and Chen et al. J. Neurosci (2009). 29(3): 600-9. Image: https://puragraft.com/products/ketamine

# Ketamine Pharmacokinetics

Onset: 15-30 seconds IV, 5-8 minutes IM

Duration of action: dose and indication dependent •

- IV generally 10-15 mins and IM generally 30-60 mins


Given IV and IM most commonly but can be given PO (poor bioavailability)

Rosenbaum et al. NIH (2022) StatPearls Ketamine

# Notable Effects

- Sedation
- Dissociation/disinhibition
- Analgesia
- Increased blood pressure
- Negative ionotropic effects
- Nausea/vomiting
- Anxiety

Rosenbaum et al. NIH (2022) StatPearls Ketamine

# Assessment Question 1

On which receptor does ketamine primarily exert its action? (choose one)

A. NMDA receptor
B. Alpha adrenergic receptor
C. Benzodiazepine receptor
D. Gamma receptor

# Assessment Question 1

On which receptor does ketamine primarily exert its action? (choose one)

A. **NMDA receptor**
B. Alpha adrenergic receptor
C. Benzodiazepine receptor
D. Gamma receptor

# Dosing

- **Analgesia**
  - **0.3mg/kg IV**
- Procedural sedation/RSI
  - 0.5-1mg/kg and 1-2mg/kg IV
- Agitation/delirium
  - 0.5-1mg/kg IV or 4-5mg/kg IM
- Super-refractory status epilepticus
  - 2+mg/kg/hr
- Depression associated with MDD
  - 0.5mg/kg IV

Rosenbaum et al. NIH (2022) StatPearls Ketamine

# Analgesia

- Goal is to provide pain relief in place of or as adjunct to opioids
- Potential for unwanted side effects despite being sub-dissociative
  - Nausea, vomiting, sedation
- Administered IV push or as 15 min infusion
  - "A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED"
- Longer term orders can run as 2-20mg/hr infusions

Motov et al. New England Journal of Medicine. (2017). 35(8).

# Analgesia Dosing Cont.

## Reduction of opioid dose needed

- Vaso-occlusive crisis

## Efficacy when opioids ineffective

- Migraines, neuropathic pain

## Post-op pain

- Evidence for reduction of not only immediate pain but also prevention of chronic pain
- Long standing chronic pain control evidence more sparse

Peltoniemi et al. Clinical Pharmacokinetics. (2016). 55:1059-1077. Image: Clipart

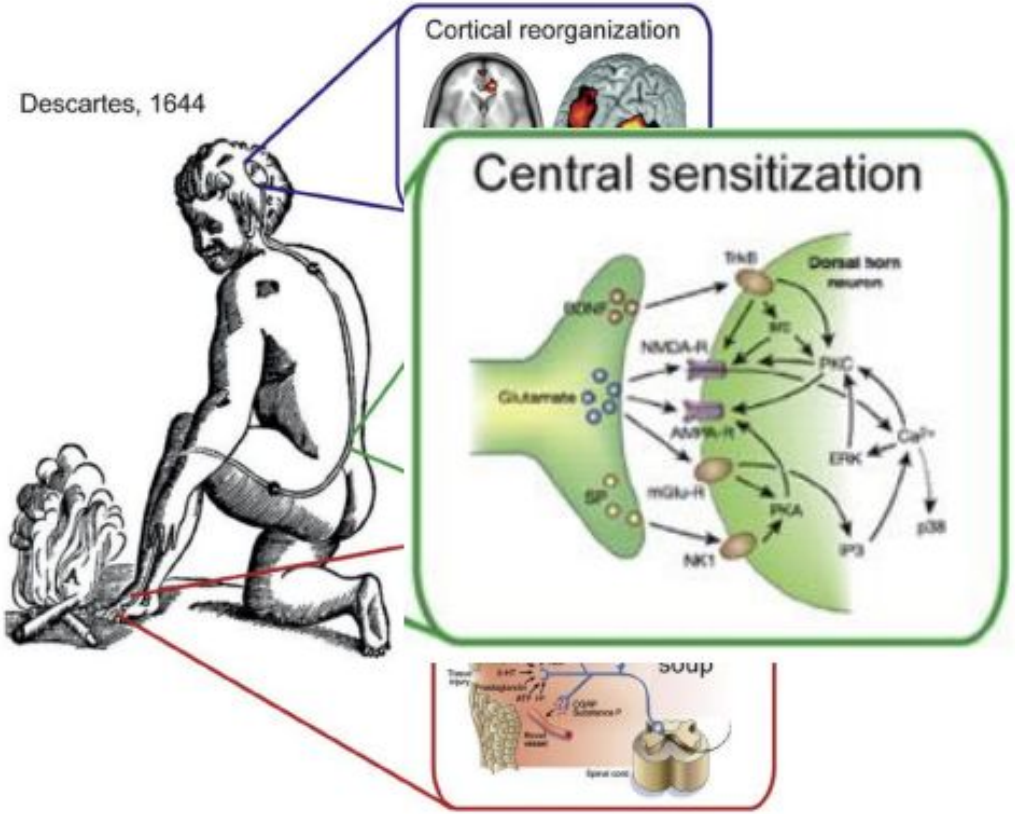



Image: http://www.nationalpain.com/central - sensitization

# Assessment Question 2

What dose of IV ketamine would you select for a 100kg patient suffering with severe pain refractory to opioids? (choose one)

A. 100mcg
B. 30mcg
C. 100mg
D. 30mg

# Assessment Question 2

What dose of IV ketamine would you select for a 100kg patient suffering with severe pain refractory to opioids? (choose one)

A. 100mcg
B. 30mcg
C. 100mg
D. **30mg**

# Dosing

- Analgesia
  - 0.3mg/kg IV
- **Procedural sedation/RSI**
  - **0.5-1mg/kg and 1-2mg/kg IV**
- Agitation/delirium
  - 0.5-1mg/kg IV or 4-5mg/kg IM
- Super-refractory status epilepticus
  - 2+mg/kg/hr
- Depression associated with MDD
  - 0.5mg/kg IV

Rosenbaum et al. NIH (2022) StatPearls Ketamine

# Procedural Sedation/RSI

- 0.5-2mg/kg pushes +/- continuous infusion
  - Can be re-dosed every ~10 minutes as needed to maintain sedation/analgesia
- Offers sedation and pain relief with minimal effect on respiratory drive
- Caution in increased intracranial or intraocular pressure states
- 0.4% patients will have laryngospasm which affects intubation conditions
  - Other side effects include excessive salivation and hypertension
- Compared to etomidate?

Si\rivilaithon et al. Sci Rep. (2023) 13:6362

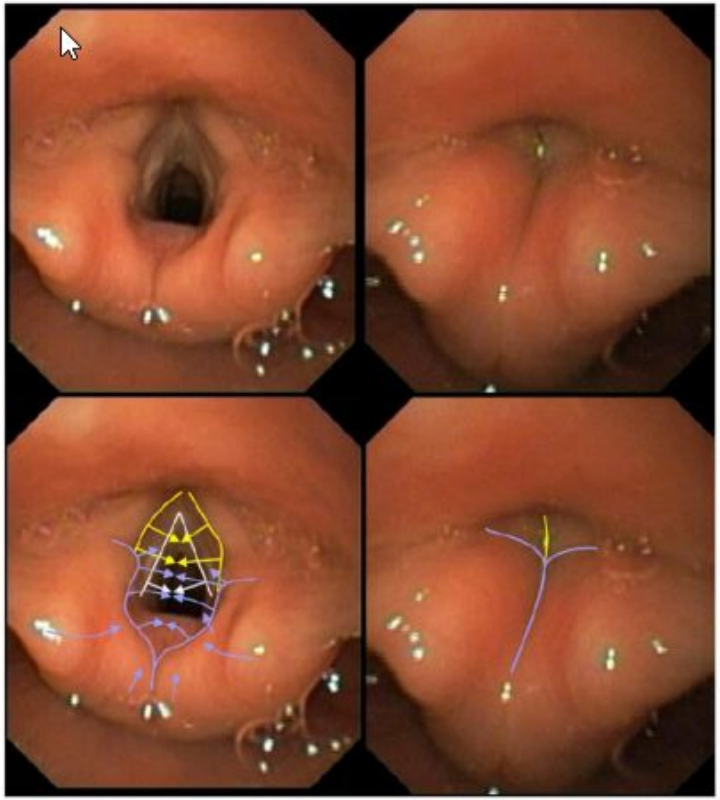
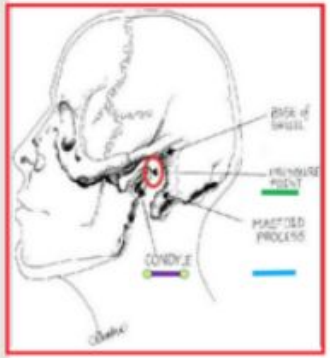


*Fig. 6. Larynx before and during a laryngospasm. White, movement of the vocal cords; yellow, movement of false cords; blue, movement of arytenoids.*

Image: https://emergencyeducation.org.au/laryngospasm/

# Laryngospasm Notch




Apply 3-5 seconds pressure
Then release for 5-10 seconds
Repeat until spasm relief

Location:
1. Behind the lobule of the pinna of each ear.
2. Anteriorly bounded by the ascending ramus of the mandible adjacent to the condyle.
3. Posteriorly by the mastoid process.
4. Cephalad by the base of the skull and external auditory canal

https://first10em.com/laryngospasm/

# Situations to Avoid Ketamine

- Hypertension
- Cardiac disease
  - Including but not limited to: MI, aortic dissection, or aneurysm
- Pregnancy or breast feeding
- Known history of schizophrenia
- Catecholamine depletion suspected*
- Concern for head trauma and/or elevated ICP**

Rosenbaum et al. NIH (2022) StatPearls Ketamine.

# Cardiac Arrest Following Ketamine Administration for Rapid Sequence Intubation

Elisabeth Dewhirst, MD, W. Joshua Frazier, MD, [...], and Joseph D. Tobias, MD ✉ (+2) View all authors and affiliations

Volume 28, Issue 6 | https://doi-org.ezp3.lib.umn.edu/10.1177/0885066612448732

Contents | PDF / ePub | Cite article | Share options | Information, rights and permissions

## Abstract

Given their relative hemodynamic stability, ketamine and etomidate are commonly chosen anesthetic agents for sedation during the endotracheal intubation of critically ill patients. As the use of etomidate has come into question particularly in patients with sepsis, due to its effect of adrenal suppression, there has been a shift in practice with more reliance on ketamine. However, as ketamine relies on a secondary sympathomimetic effect for its cardiovascular stability, cardiovascular and hemodynamic compromise may occur in patients who are catecholamine depleted. We present 2 critically ill patients who experienced cardiac arrest following the administration of ketamine for rapid sequence intubation (RSI). The literature regarding the use of etomidate and ketamine for RSI in critically ill patients is reviewed and options for sedation during endotracheal intubation in this population are discussed.

Dewhirst et al. Journal of Intensive Care Medicine. (2012) 28(6)

# On ICP

- Older studies showed an increase in ICP among patients treated with ketamine
- Newer studies found similar ICP suggest original fear overblown
- A few studies show ketamine potentially has neuroprotective tendencies

**Bottom line: Ketamine is likely safe for patients with head injuries, but out of an abundance of caution, it is reasonable to select a different medication for these patients**

Rosenbaum et al. NIH (2022) StatPeals Ketamine Image: https://tinyurl.com/4pjtx3b7

# Pediatric Considerations

- Generally safe and effective
  - Most common adverse effects are flushing or vomiting
  - Dissociation uncommon and rarely upsetting in nature
- Similar dosing to adults or 9mg/kg IN
  - Some children require higher doses or more frequent redosing
- No differences in time to discharge or rate of adverse events

M C Howes. EM Journal BMJ. (2005). 21(3) and Oliveira et al. Am J Emerg Med. (2020). 28(9): 1860-1866. Image: https://tinyurl.com/yc5h4jyz

# Emergence Reaction

- Reported in 6-12% of patients
  - Not common in pain dosing and is more a risk for procedural sedation and higher dosing levels
- Marked by extreme fear or excitement, delirium, irrational thoughts or behaviors, flashbacks, and rarely, hallucinations
- Most common in patients 18-65 years old

Rosenbaum et al. NIH (2022) StatPeals Ketamine

# Treating/Preventing Emergence Reactions

- Treat with small dose of benzodiazepine
  - Lorazepam or midazolam 1-2mg IV push recommended
- Consider coadministration with midazolam as prevention
  - Caveat: risk of respiratory depression
- Coadministration with propofol reduces risk of emergence reactions
  - “Ketofol”


| | Ketamine |
|---|---|
| Onset of Action | 30 sec (IV); 3 – 4 min (IM) |
| Peak Effect | 1 – 2 min (IV); 4 – 5 min (IM) |
| Duration of Action | 5 – 10 min (IV); 12 – 25 min (IM) |
| Advantages | Preservation Respiratory Drive & Airway Reflexes, Analgesic |
| Disadvantages | Emetogenic, Post Procedural Agitation, Elevated BP, Tachycardia |
| Inconclusive Evidence | Elevation of IOP & ICP |


| | Propofol |
|---|---|
| Onset of Action | 10 – 50 sec |
| Peak Effect | 2 min |
| Duration of Action | 2 – 5 min |
| Advantages | Ultra-Short Acting, Anti-Emetic, Anxiolytic |
| Disadvantages | Dose Dependent Hypotension, Respiratory Depression, Apnea, No Analgesia, Burns at IV site with Administration |

Images: https://www.aliem.com/ketofol-game-changer-procedural-sedation/

# Dosing

- Analgesia
  - 0.3mg/kg IV
- Procedural sedation/RSI
  - 0.5-1mg/kg and 1-2mg/kg IV
- **Agitation/delirium**
  - **0.5-1mg/kg IV or 4-5mg/kg IM**
- Super-refractory status epilepticus
  - 2+mg/kg/hr
- Depression associated with MDD
  - 0.5mg/kg IV

# Agitation and Delerium

- Agitated or combative patients routinely present to hospitals
  - Makes care and diagnosis of other ailments challenging or unsafe
- Doses of 1-3mg/kg IV or 4-5mg/kg IM
  - Recent study showed average time to sedation of 7.7 minutes using IM ketamine which was faster than haloperidol (5mg) IM (15 mins) PLUS midazolam (5mg) IM (14.7 mins)
  - Can re-dose but use caution to avoid need to intubate

Barbic et al. Annals of EM. (2021). 78(6):788-795

## Family of Colorado woman who died after paramedic injected her with ketamine sues ambulance company

The use of ketamine by emergency medical responders has drawn intense focus in Colorado

## autopsy report changed to death by ketamine

By Allison Sherry · Sep. 23, 2022, 12:02 pm

"Excited delirium" is not a valid, independent medical or psychiatric diagnosis. There is no clear or consistent definition, established etiology, or known underlying pathophysiology.

NEWS | 25 July 2018

## Controversial US ketamine trial sparks ethics complaint

**Advocacy group alleges that emergency medical workers in Minnesota gave patients ketamine injections without consent, despite known risks.**

# Assessment Question 3

Which of the following are indications for ketamine? (select all that apply)

A. Hypertensive emergency
B. Pain
C. Sedation
D. Agitation

# Assessment Question 3

Which of the following are indications for ketamine? (select all that apply)

A. Hypertensive emergency
B. **Pain**
C. **Sedation**
D. **Agitation**

# Dosing

- Analgesia
  - 0.3mg/kg IV
- Procedural sedation/RSI
  - 0.5-1mg/kg and 1-2mg/kg IV
- Agitation/delirium
  - 0.5-1mg/kg IV or 4-5mg/kg IM
- **Super-refractory status epilepticus**
  - **2+mg/kg/hr**
- Depression associated with MDD
  - 0.5mg/kg IV

# Super-refractory Status Epilepticus

- Status epilepticus that has continued for >24 hours
- Difficult to treat and associated with morbidity and mortality
- GABA mediated drug efficacy decreases d/t receptor trafficking into cell
  - NMDA receptor numbers increase

Gaspard et al. Epilepsia (2013). 54(8): 1498-1503. Shrestha et al. Indian J of Crit Care Med (2015). 19(5):283-285.

# Ketamine for Seizures

- Starting ketamine within 48 hours of determining a seizure to be refractory has shown efficacy in controlling seizures. Efficacy decreases to about 1/3 of seizures at 9 days
  - 1mg/kg bolus then 2mg/kg/hr infusion. Can be titrated up
  - Retrospective multi- center study showed rates up to 7.5mg/kg/hr to be safe
- Duration up to 14 days appears to be safe
- No difference in functional outcome

Gaspard et al. Epilepsia (2013). 54(8): 1498-1503. Shrestha et al. Indian J of Crit Care Med (2015). 19(5):283-285.

# Dosing

- Analgesia
  - 0.3mg/kg IV
- Procedural sedation/RSI
  - 0.5-1mg/kg and 1-2mg/kg IV
- Agitation/delirium
  - 0.5-1mg/kg IV or 4-5mg/kg IM
- Super-refractory status epilepticus
  - 2+m/kg/hr
- **Depression associated with MDD**
  - **0.5mg/kg IV**

Rosenbaum et al. NIH (2022) StatPeals Ketamine

# Depression and Suicidality

- Dosing: 0.5mg/kg IV over ~40 min
- Benefits seen within 90 minutes
- Duration: ~72 hours once
  - Repeated administrations leads to longer individual durations of action

Witt et al. Aust NZ J. Psychiatry (2020) 54(1):29-45, Mandal et al. Indian J Psychiatry (2019). 61(5):480-485, and Jelen et al. J Psychopharm (2021). 35(2):109-123. Im

# Definitions

Major Depression

- Five or more DSM5 symptoms for two consecutive weeks

Treatment Resistant Depression (TRD)

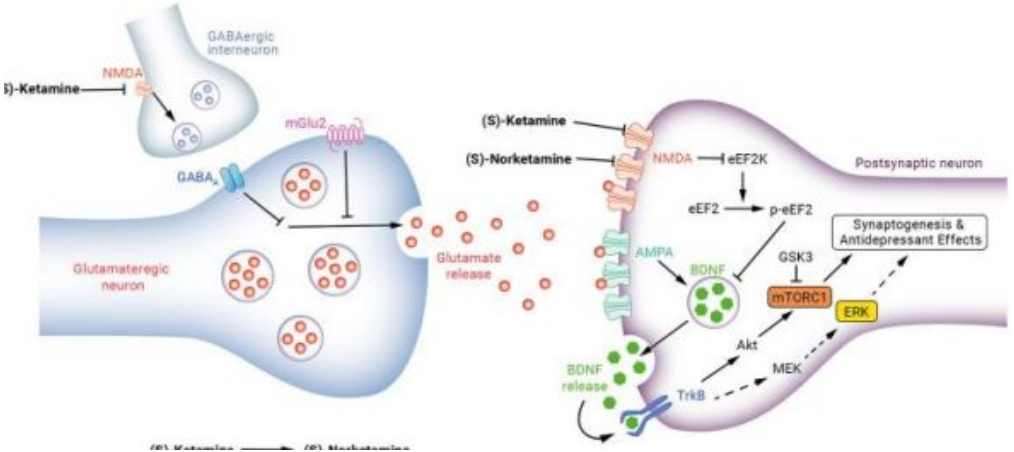
- No standard definition but usually refers to nonresponse to at least two adequately trialed, optimally dosed medications

Treatment Refractory Depression

- Also not standardized but generally patient who is nonresponsive to 5- 10 medication trials

# Proposed Mechanism of Action

Mechanistically the most convoluted but thought to be related to glutamate level surge leading to increased dopamine release as well as other downstream effects and neurologic remodeling




Witt et al. Aust NZ J. Psychiatry (2020) 54(1):29-45, Mandal et al. Indian J Psychiatry (2019). 61(5):480-485, and Jelen et al. J Psychopharm (2021). 35(2):109-123. Images: Jelen et al

# Esketamine

- FDA approved for treatment of depression
- S enantiomer • REMS
- Induction phase followed by maintenance
  - Twice per week and may eventually be decreased to q 14 days
  - Requires observed monitoring in outpatient setting

# Battle of the Formulations

- Overall, a metanalysis conducted by Bahji et al found that IV ketamine performed significantly better for MDD and BD •
  - Response and remission rates  increased
  - Dropouts due to adverse events decreased
- Esketamine has more long-term trials and evidence (FDA approved)
- ESCAPE-TRD Trial


Bahji et al. J Affect Disord. (2021). 278:542-555 Image: https://tinyurl.com/58wmxkxt

# IV Ketamine Use for Depression

- 0.5mg/kg sub-dissociative dose
- Improvement within 1 hour
  - Transient side effects
  - 6 doses over 2 weeks
    - Benefit maintained for several months
    - Some patients receive further maintenance with ketamine or typical psychotropic medications

Mandal et al. Indian J Psychiatry (2019). 480-485

# SI in the ED

- 10% of all adult patients in the ED have SI whether that is their chief complaint or not
- Traditional ED setting suboptimal for treating patients with mental health concerns- especially SI (safety and privacy concerns)
- ED overcrowding major issue
- Shortage of psychiatric beds leads to patients boarding in the ED for extended periods of time

Betz et al. Ann Emerg Med. (2016) 67(2): 276-282 and Rosenbaum Asarnow et al. Child Adolesc Psychiatr Clin N Am. (2017) 26(4): 771-783

# Ketamine for SI in the ED

- A 2015 Systematic review noted seven studies that used 0.5mg/kg over 40 mins, one study used 0.2mg/kg bolus, and a third used oral ketamine
- Earliest results seen in 40 minutes and longest lasting for 10 days
- A 2022 study found somatic symptom burden decreased compared to baseline reported by both patients and treating MDs (P<0.001 and [=0.005)
  - Feasibility highly rated by both MDs

Gaither et al. JACEP. (2022) 3(4): e12790 and Reinstatler et al. Drugs in R&D. (2015) 15: 37-43.

# Ketamine Abuse

- Death directly related to use is rare but disinhibition and delusional thinking can lead to morbidity
  - More psychological addiction risk v physical addiction
- Single dose use in the ED not associated in increased risk for ED return visit within 30 days
  - True even in more 'addiction vulnerable' patients (SUD and psychiatric illness)
  - Vulnerable patients more prone to recidivism but ketamine was not a statistically significant contributor to this

Liu et al. Brain Research Bulletin. (2016) 126(1): 68-73.

# Assessment Question 4

A single dose of ketamine in the emergency department may provide which of the following benefits to patients with suicidal ideation? (choose one)

A. A permanent cure for depression
B. Potential to allow patients to discharge home for a short period of time
C. A long-term solution for suicidal ideation
D. The ability to avoid taking other psychotropic medications

# Assessment Question 4

A single dose of ketamine in the emergency department may provide which of the following benefits to patients with suicidal ideation? (choose one)

A. A permanent cure for depression

B. **Potential to allow patients to discharge home for a short period of time**

C. A long-term solution for suicidal ideation

D. The ability to avoid taking other psychotropic medications

# Final Takeaways

- Mechanism of action is complicated and not completely understood- especially in the case of psychiatric indications
- Ketamine dosing varies by indication
- Ketamine has major utilities in the ED and beyond with uses for analgesia, sedation, depression/SI, and control of agitation despite limited official FDA approval

# CPE Instructions for:

## Ketamine: To the ED and Beyond!

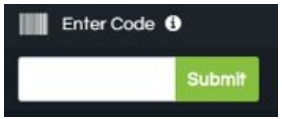
**1**

Redeem your credit online at **CEimpact.com**

*If this is the first time you have utilized the CEimpact Learning Management System (LMS) you will need to create an account.

**2**

From the **CEimpact.com** Homepage – enter the code provided in the 'Enter Code' box and click SUBMIT.




**3**

Complete the Exam & Evaluation as prompted; click SUBMIT to send your information to CPE Monitor. Follow instructions to access your CPE Statement of Credit on CPE Monitor or access your Certificate of Completion in MyCourses.

# Pharmacist Code: mM8lxO

**The deadline for obtaining your CPE Credit is 30 days from today.** The deadline is non-negotiable due to CPE Monitor reporting policies. For CME, access your certificate of completion in My Courses for this course.

# Stem Cell Transplant and Cellular Therapy Basics for the Non-Oncology Pharmacist

**Natalie Schulze, PharmD BCOP**
Senior Oncology Pharmacist
Sanford Health
Fargo, ND

# Learning Objectives

*At the completion of this activity, the participant will be able to:*

*1. State the differences between the processes related to autologous and allogeneic stem cell transplants, chimeric antigen receptor t-cell therapy (CAR-T) and bispecific antibodies.*

*2. Discuss the indication and usage of common medications utilized in stem cell transplant and cellular therapies.*

*3. Recognize potential long-term complications that can be associated with stem cell transplant and cellular therapies.*

*4. Review the pathophysiology and treatment pathways of cytokine release syndrome (CRS) and immune effector cell neurotoxicity syndrome (ICANS).*

# Abbreviations

BMT: bone marrow transplant

HSCT: hematopoietic stem cell transplant

CAR-T: chimeric antigen receptor targeting t-cell therapy

CRS: cytokine release syndrome

ICANS: immune effector cell neurotoxicity syndrome

HLA: human leukocyte antigens

CMV: cytomegalovirus

GVHD: graft-versus-host-disease

# Disclosure

Natalie Schulze has no relevant financial relationships with ineligible companies to disclose.

The off-label use of medications will be discussed during this presentation.

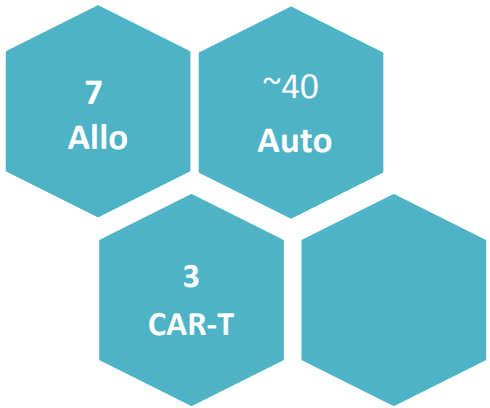
# The Basics: HSCT, CAR-T, & Bispecifics

# HSCT in North Dakota

First autologous transplant in 2021

First allogeneic transplant in 2022

First CAR-T therapy in 2023




# Why learn about stem cell transplant?

- Autologous patients can go back to their primary providers about a month following transplant
- Allogeneic patients can go back home about 3 months following transplant
- CAR-T patients can go back home about 1 month following treatment

# HSCT

## Autologous

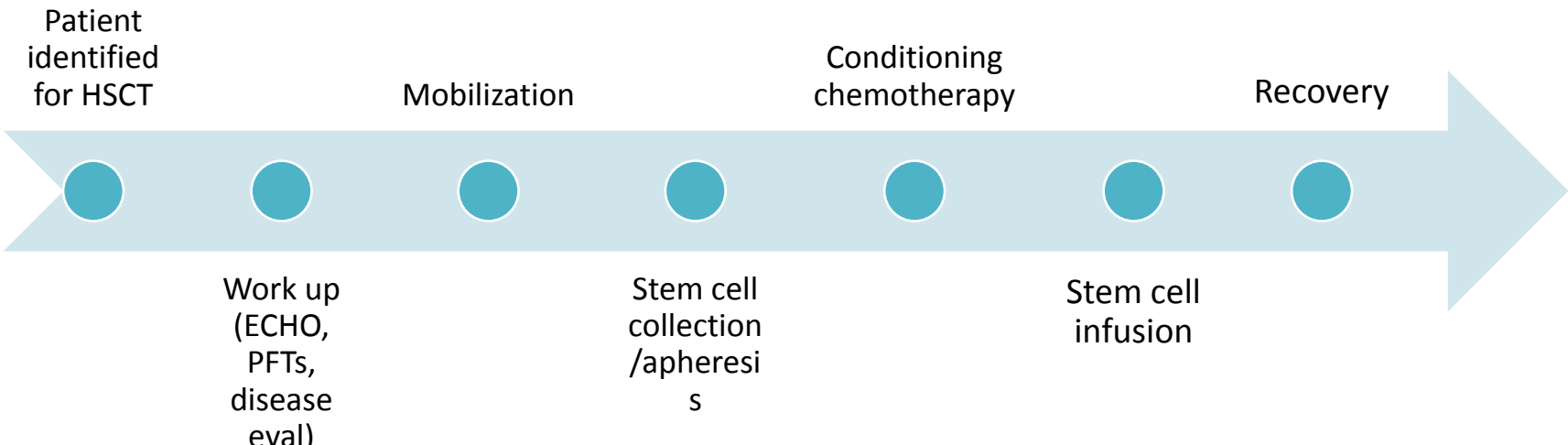
- Patient's own stem cells
- Low morbidity/mortality risk
- Utilized in multiple myeloma and lymphoma

## Allogeneic

- Donor stem cells
- Higher morbidity/mortality risk
- Primarily in leukemia
- Immunosuppression required

Vala, K. In: Beyond Fundamentals ASBMT Pharmacy SIG.2017. p. 21-87.
Copelan, EA. . N Engl J Med. 2006 April 27; 354(17):1813-1826.

# Autologous HSCT Process



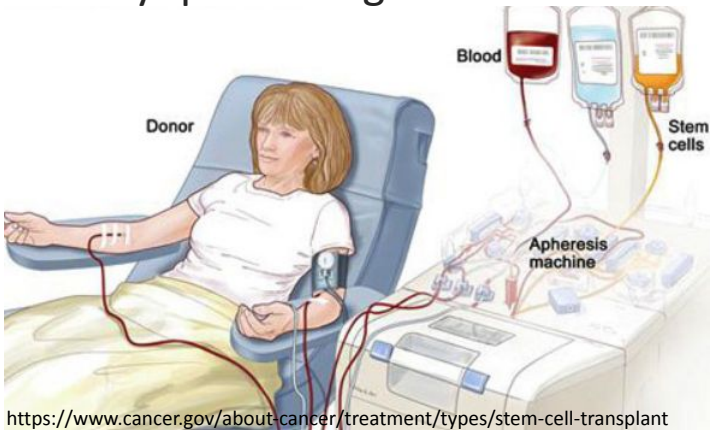
# Mobilization/Apheresis

## Mobilization

- Pushing stem cells from bone marrow into the peripheral blood
- Medications:
  - Filgrastim
  - Plerixafor

## Stem cell Collection/Apheresis

- Removing the CD34 positive cells from the peripheral blood and cryopreserving for future use




https://www.cancer.gov/about-cancer/treatment/types/stem-cell-transplant

Duong, HK. Biol Blood Marrow Transplant. 2014. 20:1262-1273.
Vala, K. In: Beyond Fundamentals ASBMT Pharmacy SIG.2017. p. 21-87

# Auto: Conditioning Chemotherapy

| | |
|---|---|
| Myeloablative | • Primary treatment of the disease for autologous transplants<br>• Fatal without stem cell rescue |
| Dose Limiting Toxicity | • Traditional chemotherapy: myelosuppression<br>• Conditioning chemotherapy: GI/pulmonary/cardiac/liver |
| Regimens | • Multiple myeloma: High dose melphalan<br>• Lymphoma: BEAM |

Jennissen C. In: Beyond Fundamentals ASBMT Pharmacy SIG.2017. p. 487-523

# Auto: Recovery

**D+10-14**

## Discharge from hospital:

- Engraftment of neutrophils & tolerating oral diet

**D+14-28**

## Monitor locally:

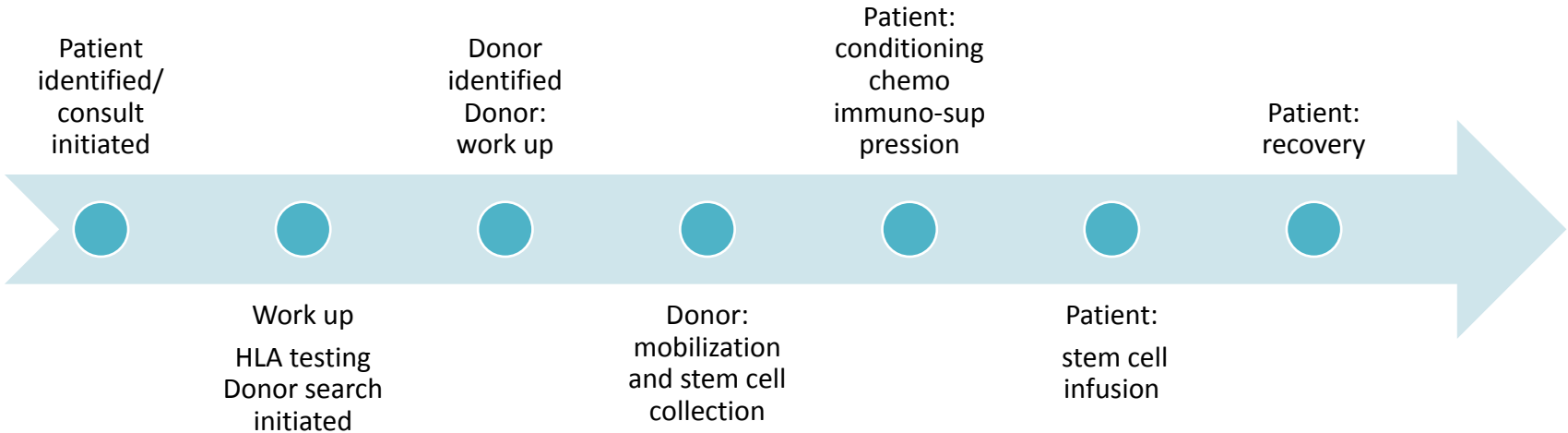
- Need for transfusions, electrolytes & tolerating oral diet

**D+28-6 mo**

## Return to home:

- Full B &T cell recovery can be up to 6 months

# Allogeneic HSCT Process



# Donor & Graft Options

- Matched sibling
- Matched unrelated
- Haploidentical
- Mismatched
- Cord blood

- Peripheral blood
- Bone Marrow
- Cord blood

Copelan, EA. . N Engl J Med. 2006 April 27; 354(17):1813-1826.
Amouzegar A. Transfusion Medicine Reviews. 2019. 33:43-50

# Allo: Recovery

**D+14-28**

## Discharge from hospital:

- Engraftment of neutrophils, tolerating oral diet & pills

**-D+100**

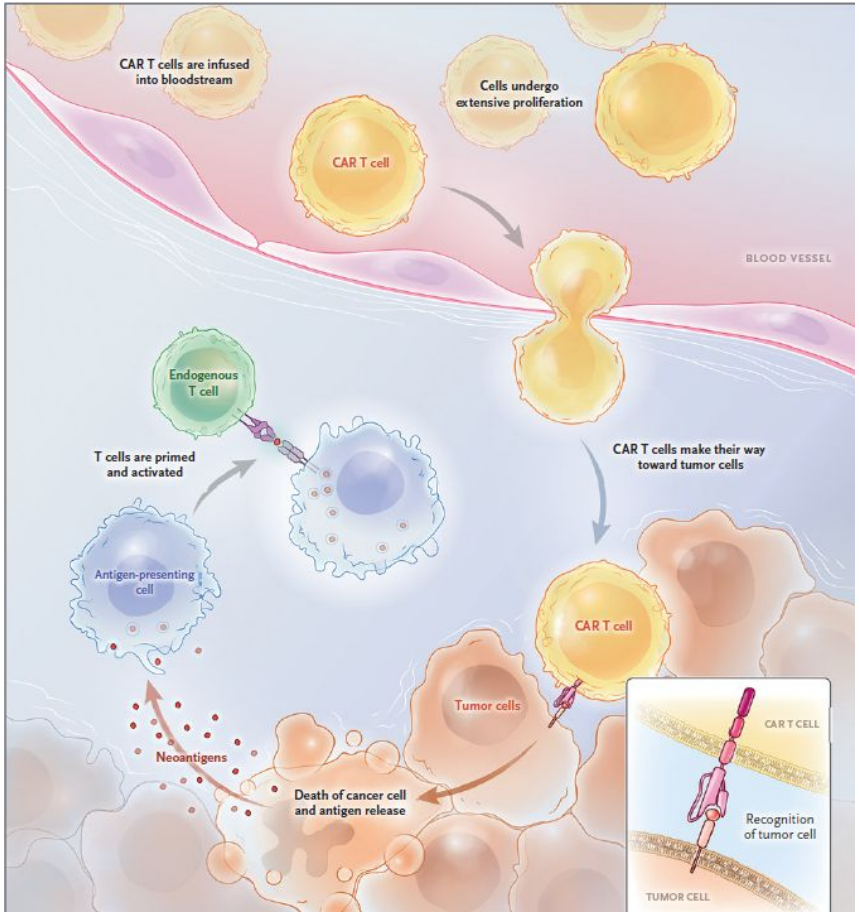
## Monitor locally:

- Need for transfusions, electrolytes, CNI monitoring, oral diet

**-1 year**

## Return to home:

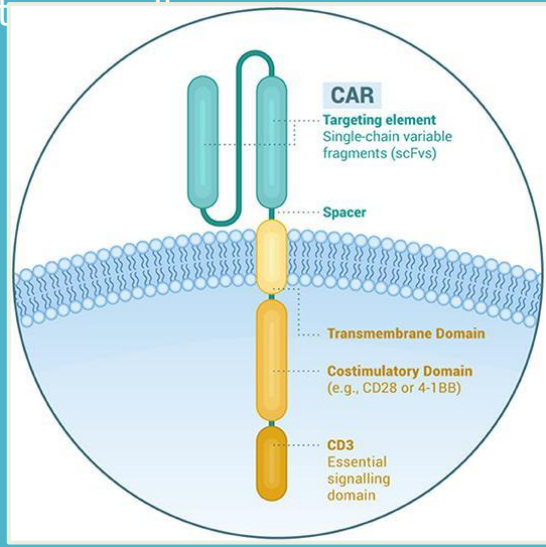
- Long term complications




June, CH. N Eng J Med. 2018; 379;1:64-73

# CAR-T

- Chimeric Antigen Receptor (CAR) T-cell Therapy
- Autologous T-cell modified to target selected antigens on t




Rodriguez Lobato et al. Front. Oncol.

# CAR-T Process

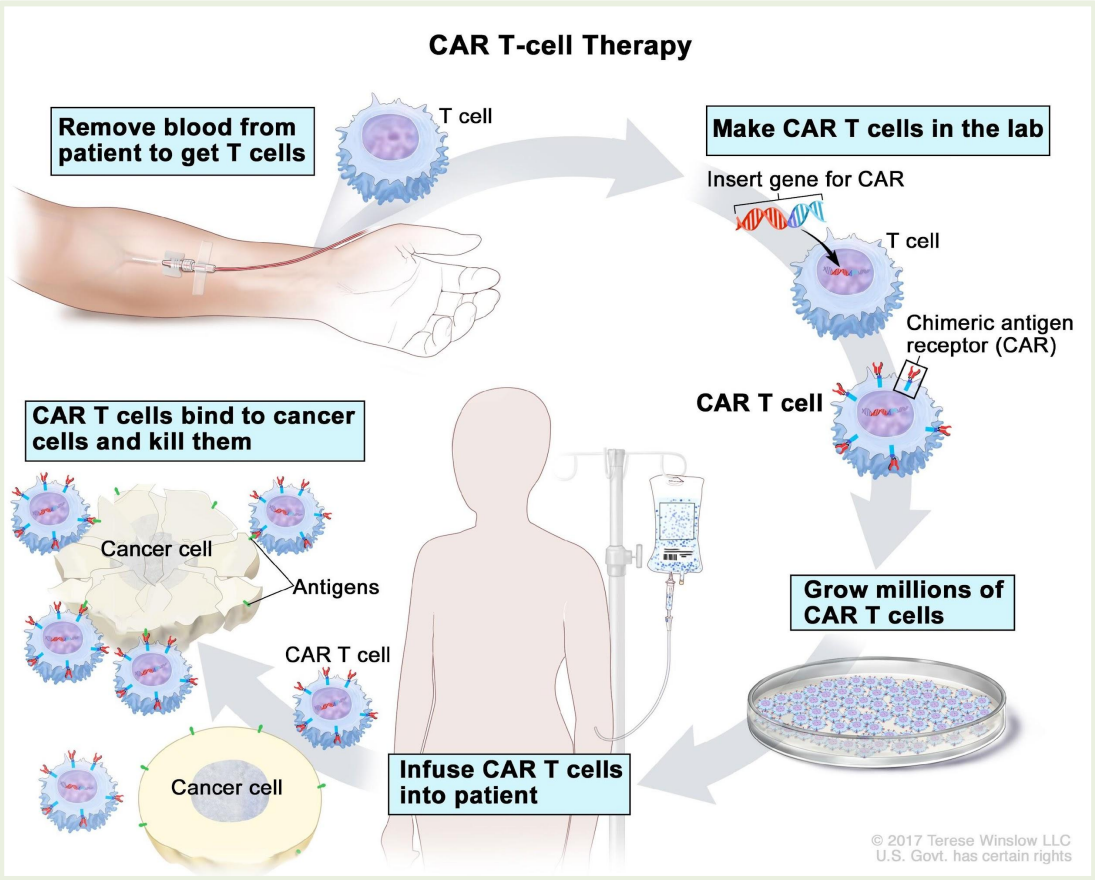



Image: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

# CAR-T Products

| CD-19 Targeting Products | FDA Approved Indications |
|---|---|
| Axicabtagene ciloleucel | Large B-cell lymphoma, follicular lymphoma |
| Brexucabtagene autoleucel | Mantel cell lymphoma, adult B-cell ALL |
| Lisocabtagene maraleucel | Large B-cell lymphoma |
| Tisagenlecleucel | Large B-cell lymphoma, pediatric B-cell ALL |
| **BCMA Targeting Products** | **FDA Approved Indications** |
| Idecabtagene vicleucel | Multiple myeloma |
| Ciltacabtagene autoleucel | Multiple myeloma |

Prescribing information: YESCARTA, TECARTUS, BREYANZI, KYMRIAH, ABECMA,

# Bispecific Antibodies

## CD19 targeting:

- Blinatumomab

## CD20 targeting:

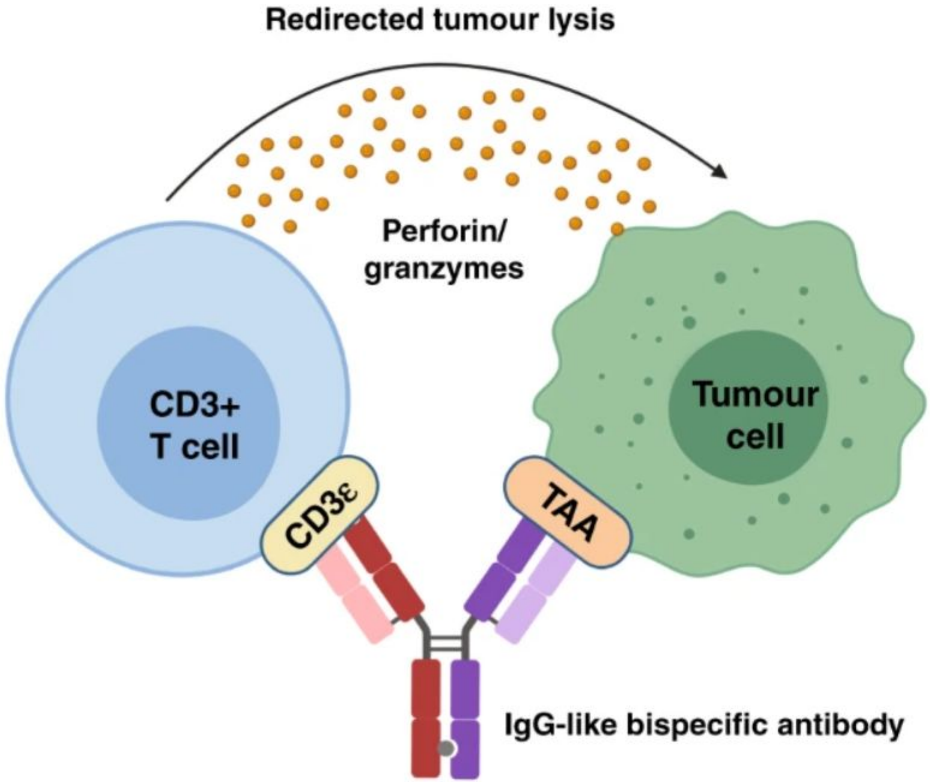
- Mosenutuzumab
- Epcoritamab
- Glofitamab

## BCMA targeting:

- Teclistamab
- Elranatamab

## GPRC5D targeting:

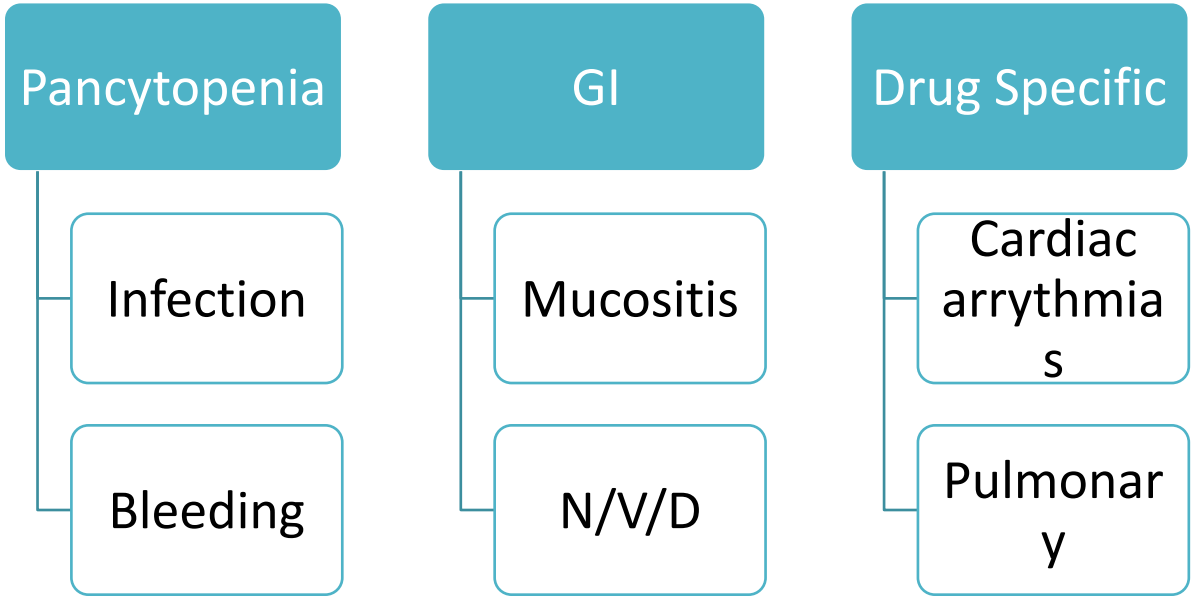
- Talquetamab




https://www.nature.com/articles/s41416-020-01225-5

# Complications: HSCT

# Complications: Auto



# Autologous: Infection

- Highest risk during WBC nadir
- Primary risk for bacterial infection
- Full B & T cell reconstitution not until ~6 months post-HSCT

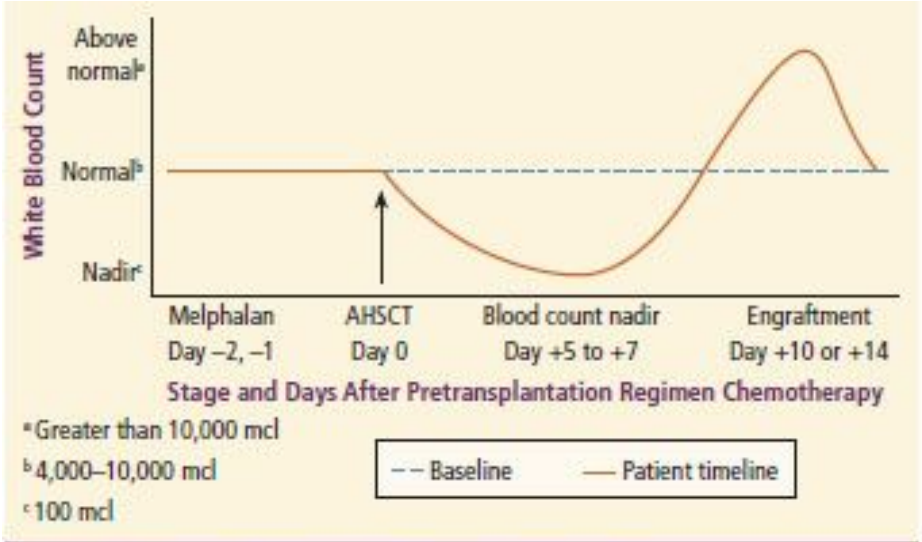
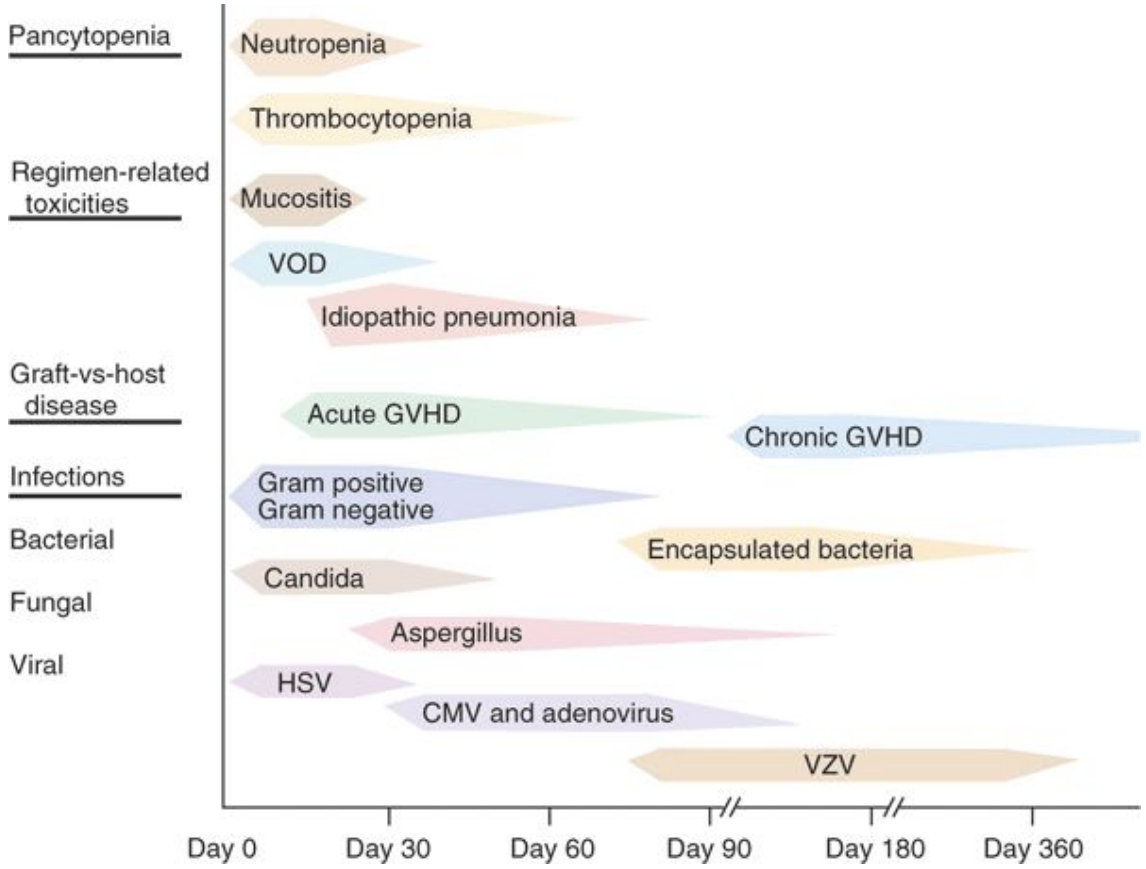



FIGURE 1. Timeline Schema for the Conditioning Regimen for Autologous Hematopoietic Stem Cell Transplantation (AHSCT)

*Note.* Based on information from Antin & Yolin Raley, 2009; Rodriguez, 2010.

Vala, K. In: Beyond Fundamentals ASBMT Pharmacy SIG.2017. p. 21-87

# Allo: Common Complications Timeline




Vala, K. In: Beyond Fundamentals ASBMT Pharmacy SIG.2017. p. 21-87

# GVHD - Acute


Donor T-cells recognize host as foreign and attack immunocompromised host

Organ systems commonly affected:
Liver, Skin, GI tract

- Treatment Grade I: Topical treatment or observation
- Treatment Grade II-IV: methylprednisolone 1-2 mg/kg/day
- Steroids tapered over 6-8 weeks

Martin, PJ. Biol Blood Marrow Transplant. 2012;18:1150-1163
Dignan, FL. British J of Hematol. 2012;158:30-45

# GVHD- Chronic


Donor T-cells play a role, but humoral immunity is also implicated

Organ systems commonly affected: ANY

- Continue or consider restarting original immunosuppressive agent
- Methylprednisolone 0.5-1 mg/kg/day
  - Tapered over 6-12 months
- Topical/inhaled steroids for skin/lung involvement

Hamilton BK. Blood. 2021:648-654

# Chronic GVHD

## High morbidity/mortality

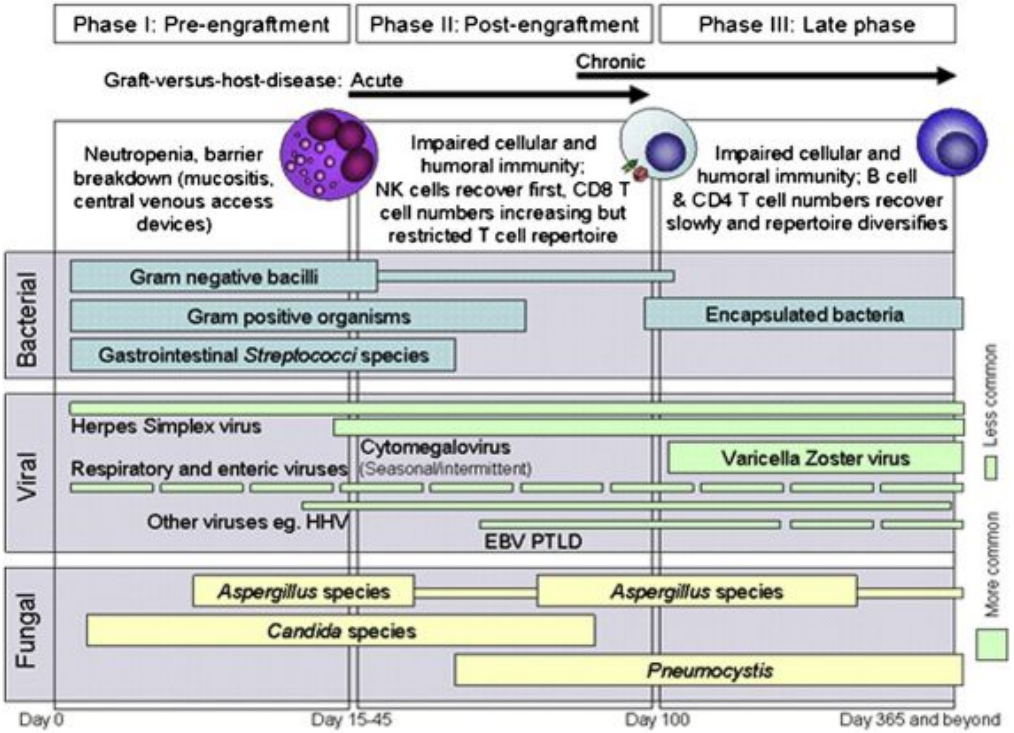
## Supportive care measures w/prolonged high dose steroid burden

- GI: proton pump inhibitor
- Bones: Calcium/vit D
- Hypertension/hyperglycemia
- Infection ppx: fungal, PCP, viral

## Secondary immunosuppressants common if steroid refractory

- Ruxolitinib, sirolimus, belumosidil

Hamilton BK. Blood. 2021:648-654




Hamilton BK. Biol Blood Marrow Transplant. 2009; 15:1143-1238

# Allo - Infection

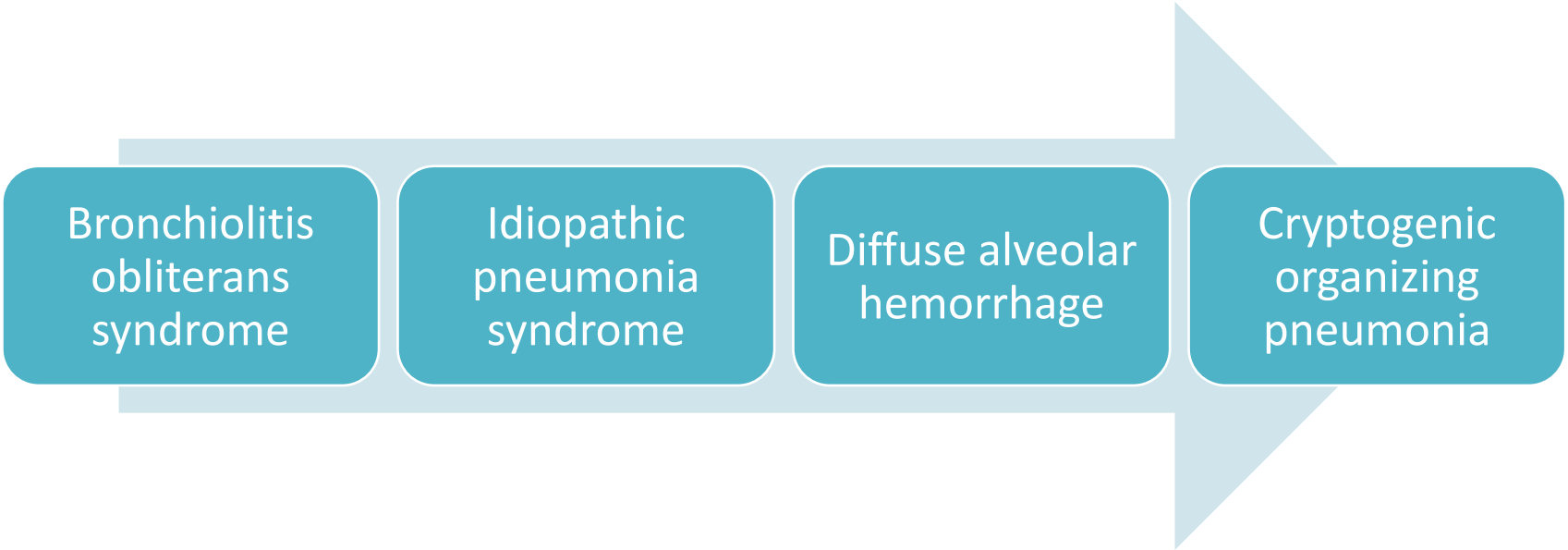
- Level of immunosuppression & presence of GVHD plays large role in risk for later phase infections

# Allo – CMV

| | |
|---|---|
| Prophylaxis | • Recipients CMV (+): consider letermovir<br>• Letermovir: 480 mg daily through D+100 |
| Monitoring | • Weekly CMV PCR through 100 days and during periods of immunosuppression |
| Treatment | • Pre-emptive treatment – ganciclovir/valganciclovir<br>• Viremia when CMV viral copies exceed threshold |

Hakki, M. Transplantation and Cellular Therapy. 2021;27:707-719

# Pulmonary Complications




Hakki, M. Transplantation and Cellular Therapy. 2021;27:707-719
Ganetsky A. Beyond Fundamentals ASBMT Pharmacy Sig. 2017. p1-32

# Allo: Long term complications

- Secondary malignancies
- Secondary solid tumors
- Post-transplant lymphoproliferative disorder
- **Cardiac and vascular complications**
- **Renal complications**
- Hepatic complications
- Pulmonary complications
- Neurological complications
- Oral complications
- Ocular complications
- **Bone complications**
- Muscle complications
- **Endocrine complications**
- Psychological complications

# Pharmacotherapy: HSCT

# Autologous - Prophylaxis

| | |
|---|---|
| Bacterial: | • Levofloxacin during neutropenia |
| Viral: | • Acyclovir or valacyclovir starting D+1 through ~12 months |
| Fungal: | • Fluconazole starting D+1 through engraftment |
| *Pneumocystis jiroveci*: | • Trimethoprim/Sulfamethoxazole 3 times per week starting at discharge through 12 months |

Hamilton BK. Biol Blood Marrow Transplant. 2009; 15:1143-1238

| Recommended Vaccine | Months Post-Stem Cell Transplant | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 months | 6 months | 8 months | 10 months | 12 months | 18 months | 24 months |
| mRNA COVID Vaccine Series | X | | | | | | |
| Diphtheria, Tetanus, acellular Pertussis (DTap, Tdap) | | X | X | | X | | |
| Haemophilus Influenza type B (Hib) | | X | X | | X | | |
| Hepatitis A | | X | | | X | | |
| Hepatitis B | | X | X | | X | | |
| Human Papillomavirus (HPV) | | If Indicated | If series started | | If series started | | |
| Inactivated Influenza | Annually X | | | | | | |
| Measles, Mumps & Rubella (MMR) | | | | | | | X |
| Meningococcal Conjugate (MCV4) | | X | X | | | | |
| Pneumococcal Conjugate (PCV-13) | | X | X | X | | If GVHD present X | |
| Pneumococcal Polysaccharide (PPSV-23) | | | | | | If no GVHD X | |
| Inactivated Polio (IPV) | | X | X | | X | | |
| Varicella (Varivax) | | | | | | | If VZV (-) |
| | | | | X | X | | |

# Post-BMT vaccinations

- All patients starting ~6 months post-HSCT
- Complete loss of immune memory with transplant

Ljungman, P. Bone Marrow Transplantation. 2009; 44:521-526

# Allo - Immunosuppression

- Immunosuppression utilized for GVHD prevention
- Typically CNI with 1-2 additional therapies
- Regimens chosen depend on:
  - Graft source, donor type, chemo regimen, and patient co-morbidities

| Calcinuerin Inhibitor (CNI) | Antimetabolite | Other |
|---|---|---|
| • Tacrolimus, Cyclosporine<br>• Backbone of immunosuppressive therapy<br>• Start tapering therapy ~D+100<br>• Through ~6 months post-HSCT | • Mycophenolate: 1000 mg PO TID D+5-+35<br>OR<br>• Methotrexate: IV D+1, 3, 8, 11 | • Cyclophosphamide (PTCY)<br>• Antithymocyteglobulin (ATG)<br>• Sirolimus<br>• Etanercept |

Luznik, L. Biol Blood Marrow Transplant. 2008; 14:641-650.
Baron F, Haematologica. 2017; 102(2):224-234.

# Allo -CNIs

## Most institutions utilize tacrolimus over cyclosporine

## IV tacrolimus commonly utilized

- Impaired GI absorption due to chemotherapy toxicity or GVHD

## Drug-drug interaction management

- Patients on and off azole antifungals

## CNI toxicities:

- Hypertension, hyperglycemia, hypomagnesemia, headache, tremor

Luznik, L. Biol Blood Marrow Transplant. 2008; 14:641-650.
Baron F, Haematologica. 2017; 102(2):224-234.

# Allo - Prophylaxis

**Bacterial** — **Levofloxacin**
- During neutropenia

**Fungal** — **Posaconazole or micafungin**
- Continue through day +100

**HSV/VZV** — **Acyclovir or valacyclovir**
- Continue for 1 year

**PCP** — **Sulfamethoxazole/Trimethoprim or Pentamidine**
- Begin after engraftment, continue for 6 months to 1 year

**CMV** — **Letermovir**
- Continue through day +100, only if recipient is CMV +

**VOD/SOS** — **Ursodiol**
- Continue through day +100

Hamilton BK. Biol Blood Marrow Transplant. 2009; 15:1143-1238

# CRS/ICANS

# What is CRS?

"Supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."

**ASTCT consensus guideline definition of CRS**

## Clinical Symptoms:

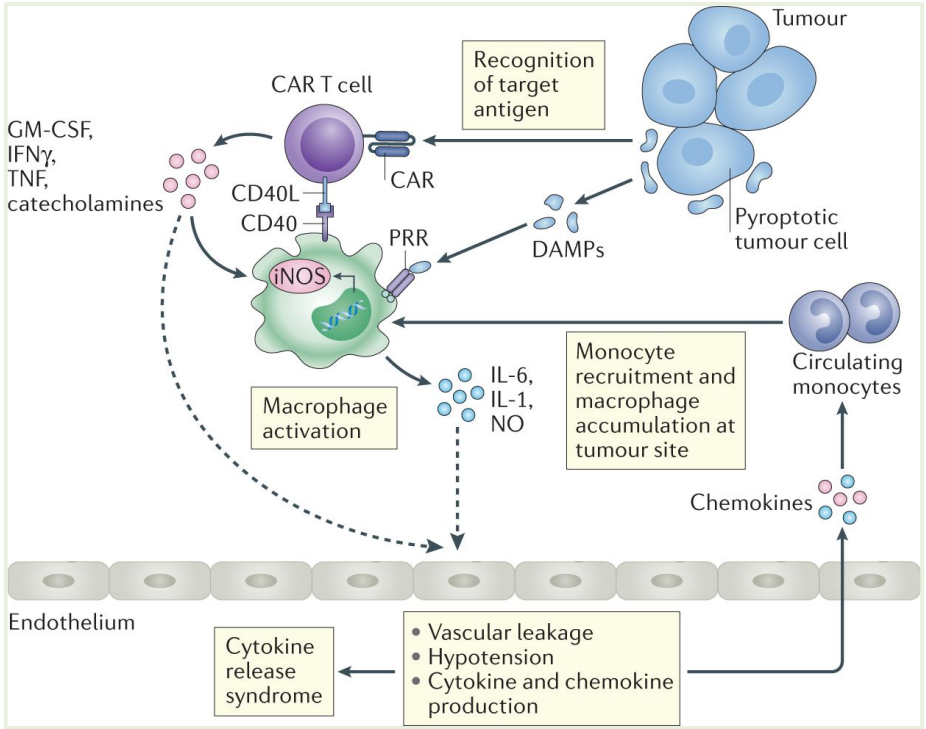
- Fever, hypoxia, hypotension
- Can progress to: cardiac abnormalities, renal failure, coagulopathy, HLH

## Lab values

- Elevations CRP, ferritin, IL-6

Lee DW. Biol Blood Marrow Transplant. 2019;25:625-638

# CRS Pathophysiology




Morris et al. Nat Review Immunol. 2022;22:85-96

# CRS - Grading

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Fever | Temperature ≥ 38°C / 100.4°F not attributable to any other cause | | | |
| Hypotension | None | Not requiring vasopressors | Requiring one vasopressor (+/- vasopressin) | Requiring multiple vasopressors (excluding vasopressin) |
| Hypoxia | None | Requiring low flow nasal cannula (≤ 6 L) or blow-by | Requiring high flow nasal cannula (>6 L), facemask, nonrebreather mask | Requiring CPAP, BiPAP or intubation and mechanical ventilation |

*Fever no longer required for Grade 2, 3, or 4 if previous treatment received

Lee et al. Biol Blood Marrow Transplant. 2019;2019:625-638

# CRS - Treatment

## Supportive care

- Acetaminophen, IV fluids, supplemental oxygen

## Tocilizumab

- Grade II or refractory Grade I

## Steroids

- Utilized after tocilizumab
- Dexamethasone

Santomasso et al. J Clin Oncol. 2021;39(35):3978-3992

# CRS – Tocilizumab

**Mechanism of action**

- Interleukin-6 (IL-6) receptor antagonist □reduction in cytokine and acute phase reactant production

**FDA approval**

- Adults and pediatric patients 2 years old with CAR T cell-induced severe or life-threatening CRS

**Dose**

- 8 mg/kg
- If <30 kg 12 mg/kg
- Maximum dose 800 mg

**Administration**

- IV infusion over 60 minutes
  - May repeat up to 3 additional doses
  - 8 hours between each dose
- Subcutaneous administration used for other indications, not CRS

ACTEMRA Prescribing information. 2017

# CRS Bispecifics vs CAR-T

**BISPECIFICS**

| Product | All Grade CRS | Grade 3-4 CRS |
|---|---|---|
| Epcoritamab | 51% | 2.5% |
| Glofitamab | 70% | 2.8% |
| Mosunetuzumab | 44% | 2.2% |
| Teclistamab | 72% | 0.6% |
| Elranatamab | 58% | 0.5% |
| Talquetamab | 76% | 1.5% |

**CAR-T**

| Product | All Grade CRS | Grade 3-4 CRS |
|---|---|---|
| Axicabtagene ciloleucel | 91-93% | 7-13% |
| Brexucabtagene autoleucel | 91% | 15% |
| Tisagenlecleucel | 45-77% | 5-22% |
| Lisocabtagene maraleucel | 42% | 2% |
| Idecabtagene vicleucel | 84% | 5% |
| Ciltacabtagene autoleucel | 95% | 5% |

Alexander et al. Transplantation and Cellular Therapy 2021;27:558-570
Chari A. N Engl J Med. 2022;387:2232-2244
Dickinson MJ. N Engl J Med. 2022; 387:2220-2231
Lesokhin A. Nature Medicine. 2023; 29:2259-2267
Morea P. N Engl J Med. 2022;387(6):495-505
Thieblemont C. J Clin Oncol. 2022; 41:2238-2247

# CRS – Treatment Pearls

- Timing:
  - **Bispecifics:** 24-48 hours following ramp up doses
  - **CAR-T:** 1-7 days post-infusion
- More trends for earlier initiation of tocilizumab
  - Prior to escalation to grade II CRS
  - Potential for decreasing duration and severity of CRS
- Utilization of steroids or tocilizumab has not been linked to compromised efficacy of CAR-T product

Banerjee R, Transplant and Cellular Therapy. 2021; 27(6):477e1-e7
Kadauke S, J Clin Oncol. 2021; 39(8):920-930

# CRS & Your facility

1. Will bispecific antibodies be utilized in your facility?
   - Growing indications in oncology
   - Potential for patients to dose escalate then transfer care
2. Do you need to stock tocilizumab?
   - For bispecific dose ramp up -> Yes
   - For patients post bispecific dose ramp up -> No
3. Are your triage staff trained to recognize CRS?

# ICANS - What

"A disorder characterized by a pathophysiologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures and cerebral edema. "

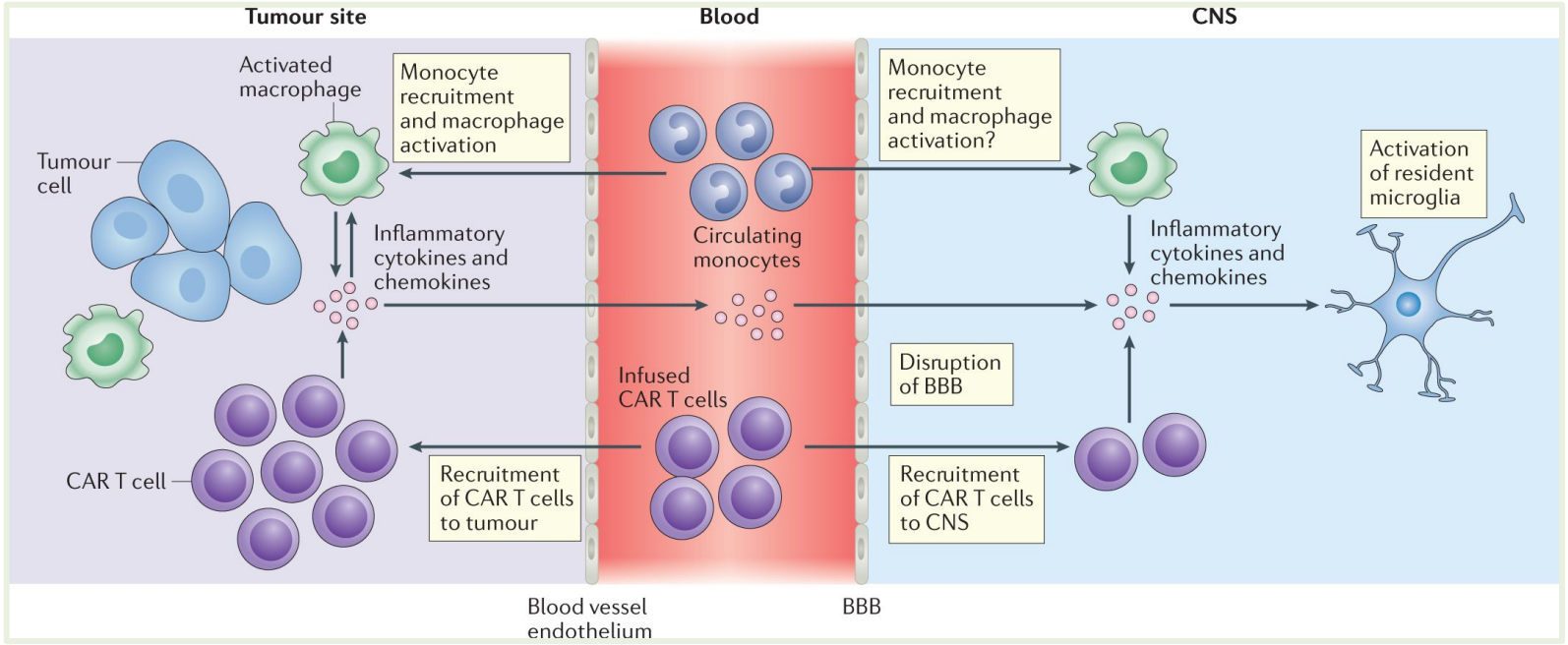
## ASTCT consensus guideline definition of ICANS

**Clinical Symptoms:**

- Broad range of neurological symptoms
- Headache, confusion, word-finding, tremors, delirium, aphasia, encephalopathy, seizures

Lee et al. Biol Blood Marrow Transplant. 2019;2019:625-638

# ICANS Pathophysiology




Morris et al. Nat Review Immunol. 2022;22:85-96

# ICANS - Grading

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| ICE Score | 7-9 | 3-6 | 0-2 | 0 (Patient unable) |
| Depressed level of consciousness | Awakens spontaneously | Awakens to voice | Awakens only to tactile stimulus | Patient unarousable, stupor or coma |
| Seizure | NA | NA | Clinical or nonconvulsive seizure on EEG that resolves rapidly | Life-threatening seizure (> 5 min) or repetitive seizures without return to baseline in between |
| Motor findings | NA | NA | NA | Hemiparesis or paraparesis |
| Elevated ICP / Cerebral Edema | NA | NA | Local edema on imaging | Diffuse edema, posturing, cranial nerve VI palsy, papilledema, Cushings triad |

Lee et al. Biol Blood Marrow Transplant. 2019;2019:625-638

# ICANS Treatment

## Supportive Care

- Levetiracetam seizure prophylaxis
- Discontinue delirium inducing medications
- Treat any underlying CRS

## Steroids

- Grade I-II: dexamethasone 10 mg IV q6-12h or methylprednisolone 1 mg/kg IV q12h
- Grade III-IV: consider escalating steroids -> dexamethasone 20 mg q6h or methylprednisolone 1000 mg IV q24h

Santomasso et al. J Clin Oncol. 2021;39(35):3978-3992

# ICANS – Bispecifics vs CAR-T

**BISPECIFICS**

| Product | All Grade ICANS | Grade 3-4 ICANS |
|---|---|---|
| Epcoritamab | 6% | 0.6% |
| Glofitamab | 4.8% | 0% |
| Mosunetuzumab | 1% | 0% |
| Teclistamab | 6% | 0% |
| Elranatamab | 3.3% | 0% |
| Talquetamab | 9% | 0% |

**CAR-T**

| Product | All Grade ICANS | Grade 3-4 ICANS |
|---|---|---|
| Axicabtagene ciloleucel | 64-69% | 28-31% |
| Brexucabtagene autoleucel | 63% | 31% |
| Tisagenlecleucel | 18-40% | 5-13% |
| Lisocabtagene maraleucel | 30% | 10% |
| Idecabtagene vicleucel | 18% | 3% |
| Ciltacabtagene autoleucel | 21% | 9% |

Alexander et al. Transplantation and Cellular Therapy 2021;27:558-570
Chari A. N Engl J Med. 2022;387:2232-2244
Dickinson MJ. N Engl J Med. 2022; 387:2220-2231
Lesokhin A. Nature Medicine. 2023; 29:2259-2267
Morea P. N Engl J Med. 2022;387(6):495-505
Thieblemont C. J Clin Oncol. 2022; 41:2238-2247

# ICANS/CRS Summary

| Grade | CRS | ICANS | CRS + ICANS |
|---|---|---|---|
| I | Supportive care<br>+/- Tocilizumab | Supportive care<br>Consider steroids | Tocilizumab |
| II | Tocilizumab | Steroids | Tocilizumab + steroids |
| III | Tocilizumab + steroids | Steroids | Tocilizumab + steroids |
| IV | Tocilizumab + high-dose steroids | High-dose methylprednisolone | Tocilizumab + high-dose methylprednisolone |

Santomasso et al. J Clin Oncol. 2021;39(35):3978-3992

# Questions?

# References


Alexander M, Culos K, Roddy J, et al. Chimeric antigen receptor T cell therapy: a comprehensive review of clinical efficacy, toxicity, and best practices for outpatient administration. Transplantation and Cellular Therapy. 2021; 27:558-570.

Amouzegar A, Dey BR, Spitzer TR. Peripheral Blood or Bone Marrow? Practical Considerations in Hematopoietic Stem Cell Transplantation. Transfusion Medicine Reviews. 2019. 33:43-50.

Banerjee R, Marsal J, Huang CY, et al. Early time to tocilizumab after B Cell Maturation Antigen directed chimeric antigen receptor T cell therapy in myeloma. Transplant and Celular Therapy. 2021; 27(6):477e1-e7

Baron F, Mohty M, Blaise D, et al. Anti-thymocyte globulin as graft-versus host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: a review from the acute leukemia working party of the European society for blood and marrow transplantation. Haematologica. 2017; 102(2):224-234.

Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med. 2022. 387:2232-2244

Copelan, EA. Hematopoietic Stem-Cell Transplant. N Engl J Med. 2006 April 27; 354(17):1813-1826.

Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022; 387:2220-2231

Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. British J of Hematol. 2012; 158:30-45.

Duong HK, Savani BN, Copelan E, Devine S, Costa LJ, Wingard JR, et al. Peripheral Blood Progenitor Cell Mobilization for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014. 20:1262-1273.

Ganetsky A. Pulmonary complications in hematopoietic cell transplant (HCT) recipients. In: Beyond Fundamentals ASBMT Pharmacy SIG. Be the Match and American Society for Blood and Marrow Transplantation 2017. p1-32

Hakki M, Aitken SL, Danziger-Isakov L et al. American society for transplantation and cellular therapy series: #3 prevention of cytomegalovirus infection and disease after hematopoietic cell transplantation. Transplantation and Cellular Therapy. 2021; 27:707-719.

Hamilton BK. Updates in chronic graft-versus host disease. Blood. 2021:648-654

Jennissen, C. Preparative Regimens in Hematopoietic Cell Transplantation. In: Beyond Fundamentals ASBMT Pharmacy SIG. Be the Match and American Society for Blood and Marrow Transplantation. 2017. p. 420-451.

June CH, Sadelain M et al. Chimeric antigen receptor therapy. N Engl J Med. 2018; 379(1):64-73.

Kadauke S, Myers RM, Li Y, et al. Risk-Adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 pediatric b-cell acute lymphoblastic leukemia: a prospective clinical trial. J Clin Oncol. 2021; 39(8):920-930

# References


Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019; 25:625-638.

Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnestisMM-3 trial results. Nature Medicine. 2023; 29:2259-2267.

Ljungman P, Cordonnier C, Einsele H, et al. Vaccination of hematopoietic cell transplant recipients. Bone Marrow Transplantation. 2009; 44:521-526.

Luznik L, O'Donnel PV, Symons HJ, et al. HLA Haploidentical Bone Marrow Transplantation for hematological malignancies using non myeloablative conditioning and high-dose posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008; 14:64`-650.

Martin PJ, Rizzo JD, Wingard JR, et al. First and Second Line Systemic Treatment of Acute Graft versus Host Disease: Recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012; 18:1150-1163

Moreau P, Garfall AL, J van de Donk NWC, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022; 387(6):495-505

Morris EC, Neelapu SS, Giavridis T, et al. Cyokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nature Reviews Immunology. 2022; 22:85-96.

Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. J Clin Oncol. 2022; 39(35): 3978-3992.

Sagar PT, Woo Ahn K, Khanal M, et al. Noninfectious pulmonary toxicity after allogeneic hematopoietic cell transplantation. Transplantation and Cellular Therapy. 2022; 28:310-320.

Thieblemont C, Phillips T, Ghesquieres H et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecfic T-cell engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. J Clin Oncol. 2022; 41:2238-2247.

Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009; 15:1143-1238.

Vala, K. Introduction to Hematopoietic Cell Transplantation. In: Beyond Fundamentals ASBMT Pharmacy SIG. Be the Match and American Society for Blood and Marrow Transplantation. 2017. p. 21-87.

# Pharmacist Question 1

SM is a 68 year old female with relapsed DLBCL s/p 2 lines of prior therapy. She just under went an apheresis procedure and he cells are being sent to the drug company for processing. Which therapy is SM most likely receiving?

A. Autologous stem cell transplant

B. Allogeneic stem cell transplant

C. Bispecific antibody

D. CAR-T therapy

# Pharmacist Question 2

JK is a 56 year old male who recently under went an allogeneic stem cell transplant. Patient had a matched unrelated donor and received tacrolimus + mycophenolate + post-transplant cyclophosphamide for GVHD prophylaxis. JK is now D+66 he has a diffuse macropapular rash covering 75% of his body and diarrhea w/3L of output per day. He is diagnosed with acute graft versus host disease after GI biopsy. What is the most appropriate initial treatment?

A. Methylprednisolone 1 mg/kg q 12 hours

B. Infliximab 5 mg/kg x1

C. Observation

D. Ganciclovr 5 mg/kg q12h

# Pharmacist Question 3

Which of the following statements is TRUE regarding tacrolimus use following allogeneic stem cell transplant?

A. Tacrolimus use is life-long in allo patients

B. Commonly make adjustments for drug-drug interactions

C. Patients often have high magnesium levels

D. IV tacrolimus is never used

# Pharmacist Question 4

LM is a 65 year old male s/p therapy with axicabtagene ciloleucel. Today is D+2 in the last several hours he has developed 102 fevers, and most recent blood pressure was found to be 85/69. What are the appropriate next steps for treatment of his CRS?

A. Fluid bolus, consider tocilizumab 8 mg/kg

B. Methylprednisolone 1 mg/kg x1

C. Cefepime 2 gm q8h

D. Ursodiol 300 mg TID

# CPE Instructions for:

## Stem Cell Transplant and Cellular Therapy Basics for the Non-Oncology Pharmacist

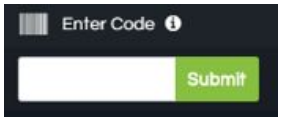
**1**

Redeem your credit online at **CEimpact.com**

*If this is the first time you have utilized the CEimpact Learning Management System (LMS) you will need to create an account.

**2**

From the **CEimpact.com** Homepage – enter the code provided in the 'Enter Code' box and click SUBMIT.




**3**

Complete the Exam & Evaluation as prompted; click SUBMIT to send your information to CPE Monitor. Follow instructions to access your CPE Statement of Credit on CPE Monitor or access your Certificate of Completion in MyCourses.

# Pharmacist Code: xhl1ng

**The deadline for obtaining your CPE Credit is 30 days from today.** The deadline is non-negotiable due to CPE Monitor reporting policies. For CME, access your certificate of completion in My Courses for this course.

Bugs and Drugs: NDSHP Clinical Pearls:

# Implementation of a Pharmacy-Managed Probiotic Protocol to Reduce the Incidence of Clostridioides difficile Infection

Chip Vang, Pharm.D., PGY1 Pharmacy Resident

Terry Altringer, Pharm.D., Clinical Pharmacy Supervisor

# Disclosures

- Neither presenter have any relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

*At the completion of this activity, the participant will be able to:*

***1. Identify the potential benefits associated with probiotics in reducing antibiotic associated diarrhea and C. difficile.***

***2. Outline how to incorporate a pharmacist-managed probiotic protocol.***

*3. Determine the appropriate treatment for an ESBL and AmpC bacteria.*

*4. Compare and contrast the differences between how to classify a bacteria as ESBL or AmpC.*

*5. Examine treatment options available for beta blocker and calcium channel blocker toxicity.*

*6. Discuss the difference between time-dependent and concentration dependent antibiotics.*

*7. Review lengths of infusion rates to determine appropriate length type of infusion.*

*8. Classify patient population with a consensus recommendation for prolonged infusions vs. short infusions of beta-lactams.*

# Definitions

- **Antibiotic-associated diarrhea (AAD):** Diarrhea that develops in a person who is taking or recently took antibiotics.
- **C. Difficile (Clostridioides difficile):** an anaerobic, gram-positive, spore-forming bacterium which may infect human hosts after antibiotic disruption of normal gut flora. C. difficile releases toxins that damage the intestinal mucosa resulting in diarrhea, abdominal pain, fever, and bloody stool.
- **Microbiome**:
    - Normal microbiome, or normal gut flora, contains millions of bacteria and serve a significant role in host protection and immunity.
    - The microbiome controls barrier protection, digestive & absorptive functions, immune modulation, neuroendocrine communication, and nutrient production.
    - Antibiotics can alter the hosts "good" bacteria, resulting in flourishing of potentially harmful bacteria, including C. difficile.
- **Probiotics:** live microorganisms that are intended to have health benefits when consumed or applied to the body [1]

# Background

- Diarrhea is one of the most common side effects of antibiotic use, with a reported incidence as high as 35%. Incidence tends to be higher in hospitalized patients including those of older age, co-morbidities, or factors that interrupt protective effects of the gut barrier [2-3]
- In the U.S. in 2017, nearly 500,000 cases of CDI were reported resulting in over 20,000 deaths and at a cost of between $5.4-6.3 billion dollars, annually [4].
- According to the CDC, C. difficile is considered one of the greatest threats in antimicrobial resistance [5]

# Background (cont'd)

- Hospital-acquired *C. difficile* is considered an avoidable event.
- Trinity Health had a higher incidence of hospital-acquired *C. difficile* infections as reported by NHSN (FY2022 = 20 cases).
- Trinity Health's Strategic Deployment Plan (SDP) quality process targeted CDI as a fiscal year initiative, for which a multidisciplinary team was assembled.
- One of the primary initiatives recommended by the team was to implement a probiotic protocol. This recommendation was tasked to the Antimicrobial Stewardship Team for operationalization.

# Evidence

- **Important concepts**:
  - Not all probiotic strains are created equal, and some strains elicit specific benefits.
  - Controlled trials have helped elucidate strains that might be effective.
  - If we think of probiotics like antibiotics, we select the correct strain with proven benefits for the specific disorders.

- Multiple clinical trials have confirmed the efficacy of probiotics in the treatment of antibiotic-associated diarrhea, but does that translate to prevention of CDI[(6)]?

# Evidence

| Author | Study Details | Formulation (Strains) | Results | Comments |
|---|---|---|---|---|
| Hickson, et al. (7) | Randomized, Double-Blind, Placebo-controlled Trial.<br><br>N=135 | Probiotic yogurt drink containing<br>• *L. casei*<br>• *S. thermophilus* and<br>• *L. bulgaricus* | Significant reduction in the incidence of AAD (P=0.007) and CDI (P=0.001) | Drinks ingested within 48 hours of antibiotics. |
| Beausoleil, et al. (8) | Prospective, randomized, double-blind, placebo-controlled trial<br><br>N=89 hospitalized patients | • *L. acidophilus*<br>• *L. casei* | AAD: 15.9% vs. 35.6% (P=0.05) and 8-day LOS vs. 10 days.<br>CDI: 2.5% vs. 15.5% (P=0.06) | Hospitalized<br><br>Patients had taken at least 3 days of any systemic antibiotic. |
| Can, et al. (9) | Double-blind controlled study<br><br>N=151 | *S. boulardii* | AAD: 2.4% vs. 9% (p<0.05) | Patients received any systemic antibiotic.<br>No serious side effects occurred. |
| Gao, et al. (10) | Randomized, double-blind, placebo-controlled, dose-ranging study.<br><br>N=255 | 3 groups:<br>• Probiotic mixture of *L. acidophilus* and *L. casei* containing 100 billion CFU/mL,<br>• Probiotic mixture containing 50 billion CFU/mL<br>• Placebo | AAD: 15.5% in the high dose group, vs. 28.2% in the lower dose group vs. 44.1% for placebo (P<0.001).<br><br>CDI: 1.2% in the high-dose group and 9.4% in the low-dose group. | Probiotics began within 36 hours of initial antibiotic administration. |
| Wombell et al. (11) | Retrospective cohort study<br><br>N=8,763 | *S. Boulardii* 20 billion CFU's per day | Hospital-Onset CDI includence 0.56% in S. bouldardii group, vs. 0.82% in non-treated patients (p=0.035) | The authors concluded that prophylaxis with S. bouldardii reduced the incidence of HO-CDI in patients on CDI-associated antibiotics. |

# Mechanism

Proposed mechanism of probiotics [12] :

- Enhancement of gut epithelial barrier
- Increase adhesion to intestinal mucosa
- Competitive exclusion of pathogenic microorganisms
- Production of antimicrobial substances
- Immunomodulatory effects
  - Increased IgA secretion
  - Increased IL-10 production
- Downregulation of Toll-Like Receptors thereby suppressing gut inflammation

# Protocol

- Protocol developed by the Antimicrobial Stewardship Team and subsequently approved by the P&T Committee and Medical Executive Committees of Trinity Health.

- Protocol launch July 2022.
- **Inclusion**: Adult patients receiving high-risk antibiotics

- **Exclusions**:
  - Short duration high-risk antibiotic use (examples: Once, Pre-Op, Post Op, ETC doses, ≤ 72hr duration)
  - Currently taking probiotics (if only one of the protocol probiotics is ordered, pharmacist will add the other)
  - *Patients in ICU*
  - *Patients with central lines*
  - NPO and/or receiving TPN
  - Acute flare of Inflammatory Bowel Disease or Irritable Bowel Syndrome
  - Abdominal surgery (pending or recent)
  - Known previous infections with C. difficile in the previous 90 days
  - Immunocompromised condition and undergoing active treatment

# Protocol (cont'd)

- Immunocompromised [13] :

Patients are considered to be moderately or severely immunocompromised due to several types of conditions and treatments. This is not an exhaustive list. Examples include:

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received chimeric antigen receptor (CAR)-T-cell therapy (a treatment to help your immune system attach to and kill cancer cells) or received a stem cell transplant (within the last 2 years).
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Advanced (CD4<50 cells/uL) or untreated HIV infection (i.e., CD4 T-cell count <200 cells/uL).
- Active treatment with high-dose corticosteroids (e.g., >20mg/day prednisone or equivalent per day when administered for $\geq$ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, biologic agents that are immunosuppressive or immunomodulatory, or other drugs that may suppress the immune response.

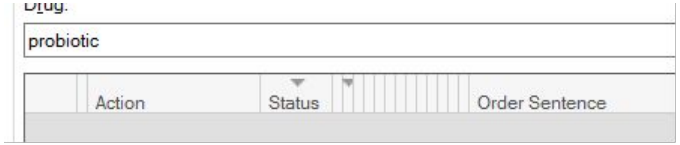
# Protocol (cont'd)

- Per protocol, Pharmacy will automatically order the following probiotics with the initial high-risk antibiotic order:
- Florastor (Saccharomyces boulardii) 250mg twice daily x10 days, AND
- Culturelle (Lactobacillus rhamnosus (GG)) 1 capsule daily x10 days

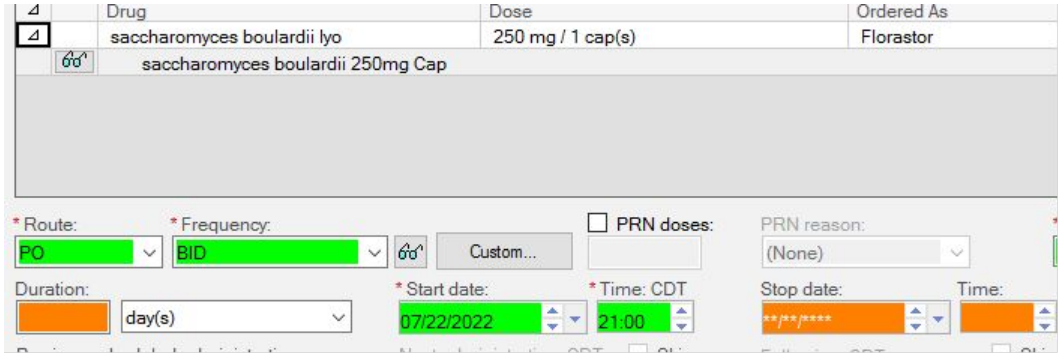
- **NOTE**: A general recommendation is to continue probiotics for a total of 7 days after completion or discontinuation of the high-risk antibiotic(s). It is the discretion of the discharging provider to continue probiotics upon patient discharge. Patients may be encouraged to purchase and/or continue probiotics at home.
- Duration will be antibiotic duration + 7 days.
- Probiotics will be discontinued if high-risk antibiotic is discontinued prior to reaching its hard stop duration.
- If no H&P or patient information is available, pharmacist will use the pharmacy intervention form and **save** so it populates the MPTL with a **pending task** for shift handoff if evaluation was not able to be completed at the time of order verification.

# Protocol (cont'd)

- Ordering Process occurs via  Order Set:
- Search Bar




- The order set will open with it's two med orders, both included.  Select OK

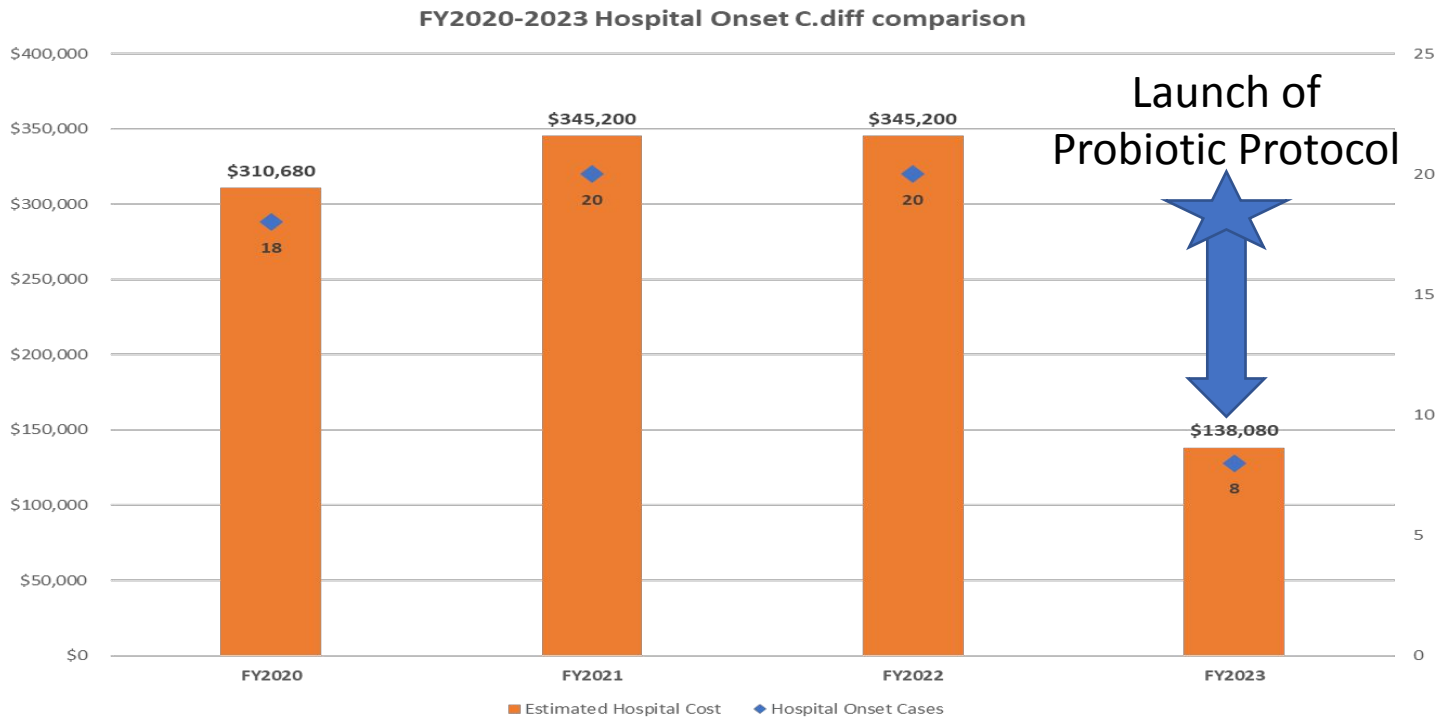
# Protocol (cont'd)

| Antibiotic Class | Products |
|---|---|
| Beta-lactam/Beta-lactamase inhibitor combos | Amoxicillin/clavulanate<br>Ampicillin/sulbactam<br>Piperacillin/tazobactam<br>Ceftolozane/tazobactam<br>Ceftazidime/avibactam |
| Carbapenems | Ertapenem<br>Imipenem<br>Meropenem<br>Meropenem/vaborbactam |
| Cephalosporins (IV and oral) | Cefpodoxime<br>Ceftriaxone<br>Ceftazidime<br>Cefepime<br>Ceftaroline |
| Fluoroquinolones (IV and oral) | Ciprofloxacin<br>Levofloxacin |
| Lincomycin derivatives | Clindamycin |

# **Findings**:

- Snapshot of protocol utilization between July 1, 2022 – December 31, 2022.
- N=161 patients treated per protocol, with 1,874 doses of probiotic administered.
- Average number of doses ~ 11/patient (or, ~ 5 days of treatment).
- Total probiotic investment ~$1,000.

# Findings




*Estimated $17,260 per hospital onset C.diff infection (ahrq.gov)

# Probiotic Safety [14-16]

- No reports of adverse effects to probiotics since protocol activation.
- In general, probiotics are well tolerated.
- Gas, bloating, and abdominal discomfort most common side effects.
- Allergic reactions may be associated with various inert ingredients (lactose, milk proteins, gluten, etc.)
- Secondary infections from pathogenic bacterial contaminants
- Secondary infections (Saccharomyces fungemia or Lactobacillus bacteremia).

# In Conclusion

- C. difficile infections are associated with much morbidity, mortality, and expense.
- Clinical studies evaluating probiotics signal potential benefit in reducing the incidence of AAD and CDI.
- More data is needed to identify which probiotic strains are most effective, what the optimal CFU dose is, and timing & duration of administration.
- Trinity's experience implementing a pharmacist-managed probiotic protocol has been positive, albeit from an observational perspective. Time will tell whether the benefit persists.

# Questions

# References


1. National Center for Complementary and Integrative Health. Probiotics: What you need to know. Probiotics: What You Need To Know | NCCIH (nih.gov). Accessed October 19, 2023.
2. Hong Zhou, Qiang Xu, Yu Liu, Li-Tao Guo. Risk factors, incidence, and morbidity associated with antibioticassociated diarrhea in intensive care unit patients receiving antibiotic monotherapy. World J Clin Cases 2020 May 26; 8(10): 1908-1915.
3. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of Clostridioides difficile infection and outcomes. N Engl J Med. 2020;382:1320–1330.
4. Zhang S, Palazuelos-Munoz S, Balsells EM, et al. Cost of hospital management of Clostridium difficile infection in United States-a meta-analysis and modelling study. BMC Infect Dis. 2016;16:447.
5. Centers for Disease Control. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.. Available at: www.cdc.gov/drugresistance/biggest-threats.html.
6. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients-A Systematic Review and Meta-Analysis. Antibiotics 2017, 6,21.
7. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic lactobacillus preparation to prevent diarrhea associated with antibiotics: randomized double-blind placebo-controlled trial. BMJ 2007;335:80.
8. Beausoleil M, Fortier N, Guenette S, et al. Effect of a fermented milk combining lactobacillus acidophilus CL1285 and lactobacillus casei in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. Can J Gastroenterol 2007;21(11):732–6.
9. Can M, Beşirbellioglu BA, Avci IY, Beker CM, Pahsa A. Prophylactic Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea: a prospective study. Med Sci Monit. 2006;12(4):19-22.
10. Gao XW, Mubasher M, Fang CY, et al. Dose-response efficacy of a proprietary probiotic formula of lactobacillus acidophilus CL1285 and lactobacillus casei LBC8oR for antibiotic-associated diarrhea and clostridium difficile-associated diarrhea prophylaxis in adult patients. Am J Gastroenterol 2010;105:1636–41.
11. Wombell E, Patterson ME, Bransteitter B, Gillen LR. The Effect of Saccharomyces boulardii Primary Prevention on Risk of Hospital-onset Clostridioides difficile Infection in Hospitalized Patients Administered Antibiotics Frequently Associated With C. difficile Infection. Clin Infect Dis 2021;73(9):2512–8.
12. Burmudez-Brito M, Plaza-Diaz J, Munoz-Quezada S, Gomez-Llorente C, Gil A. Probiotic Mechanism of Action. Ann Nutr Metab 2012;61:160–174.
13. People Who Are Immunocompromised. www.cdc.gov/coronavirus/2013-ncov/need-extra-precautions/people-who-are-immunocompromosed.html. Accessed 10/18/2023.
14. Patel R, DuPont H. New Approaches for Bacteriotherapy: Prebiotics, New-Generation Probiotics, and Synbiotics. Clin Infect Dis. 2015 May 15; 60(Suppl 2): S108–S121.

*Bugs and Drugs: NDSHP Clinical Pearls*

# When the Heart Tox: Beta Blocker and Calcium Channel Blocker Toxicity

Tatianna Pollak, PharmD
Pharmacist, Essentia Health-Fargo
27 October 2023

# Disclosures

Tatianna Pollak has no financial relationships relevant to this presentation to disclose.

# Learning Objectives

At the competition of this activity, the participant will be able to:

1. *Identify the potential benefits associated with probiotics in reducing antibiotic associated diarrhea and C.difficile.*
2. *Outline how to incorporate a pharmacist-managed probiotic protocol.*
3. *Determine the appropriate treatment for an ESBL and AmpC bacteria.*
4. *Compare and contrast the differences between how to classify a bacteria as ESBL or AmpC.*
5. ***Examine treatment options available for beta blocker and calcium channel blocker toxicity.***
6. *Discuss the difference between time-dependent and concentration dependent antibiotics.*
7. *Review lengths of infusion rates to determine appropriate length type of infusion.*
8. *Classify patient population with a consensus recommendation for prolonged infusion vs. short infusion of beta-lactams.*

# Patient Case Introduction

MM is a 30 year old female brought into the emergency department after ingesting 30 tablets of her amlodipine 10 mg refill four hours ago.

# Toxic Exposure Report (2020)

- Cardiovascular drug exposure: 6th most common category
- Fatalities reported
  - Beta blockers: 122
    - Single substance exposure: 12
  - Calcium channel blockers: 176
    - Single substance exposure: 41

***Case 2863. Acute-on-chronic verapamil ingestion: undoubtedly responsible***

**Scenario/Substances:** A 78 y/o female presented to the ED weak and dizzy after an taking 50 verapamil ER 100 mg tablets 12 h prior in a suicide attempt.

**Past Medical History:** Hypertension, DM, depression, verapamil ER, losartan, citalopram, linagliptin, clopidogrel, conjugated estrogens, "statin".

**Physical Exam:** Drowsy. BP 88/55, HR 60, $O_2$ sat 99% on RA.

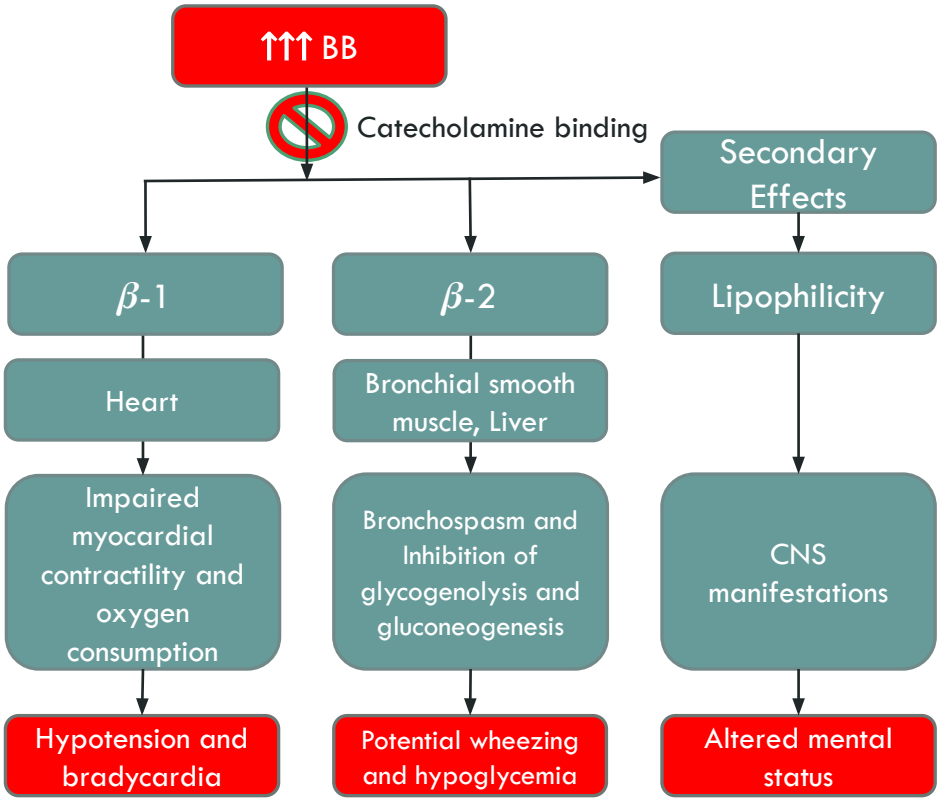
**Laboratory/Diagnostic Findings:** Na 139/K 4.9/Cl 102/$CO_2$ 22/BUN 26/Cr 2.01/Glu 297, lactate 1.6 mmol/L, AST 44, ALT 28 Serum APAP, ethanol and salicylate not detected.

**Clinical Course:** She was hypotensive and bradycardic in the ED and complained that her legs were hurting. In the ICU, she developed a HR 30 and complete heart block. She received calcium and atropine. She went into cardiac arrest and was intubated and placed on a ventilator. She received insulin 70 units IV bolus but no insulin infusion. Transcutaneous pacer was applied. Vasopressors, dextrose, and sodium bicarbonate were administered. She became hypothermic and her $O_2$ saturation dropped to 60%. She had a second cardiac arrest. ILE was administered. Patient died 5 h after her arrival to the ICU.

**Autopsy Findings:** Toxicology on pre mortem blood: verapamil 1900 ng/mL. Cause of death: acute verapamil intoxication. Manner of death: suicide.

Gummin DD, 2021.

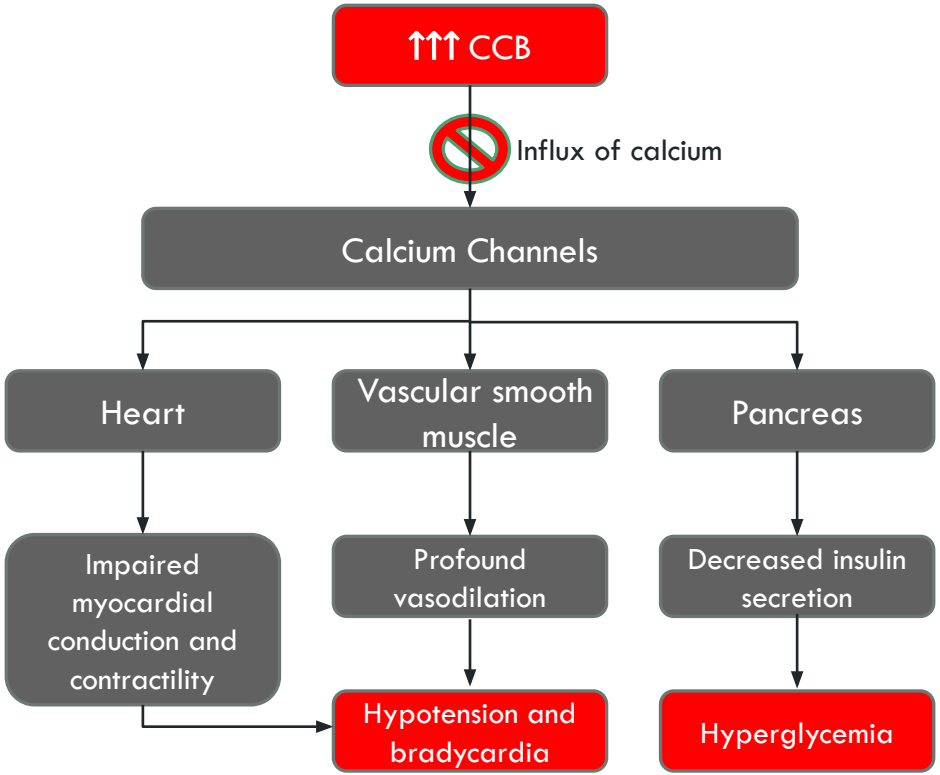
# Beta Blocker Toxicity




BB selectivity is diminished at toxic levels

Lashari BH, 2018.

# Calcium Channel Blocker Toxicity




CCB selectivity is diminished at toxic levels

Lashari BH, 2018.

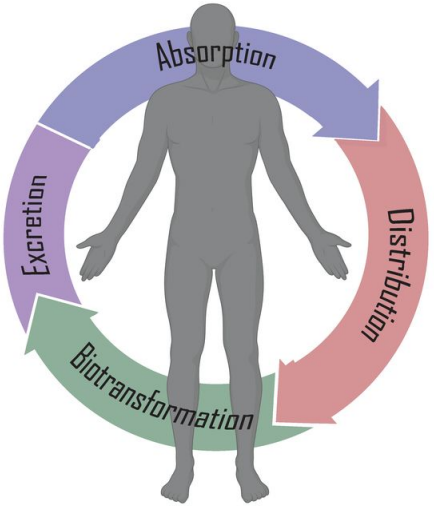
# Approach to a Patient with Toxic Exposure

- Agent ingested
- Amount ingested
- Time of ingestion
- Co-ingestions
- Clinical presentation
- Vitals
- Past medical history
- Early therapy management
- Consult Poison Control Center

Hoffman RS, 2015.

# Toxicokinetics

| Toxicokinetics ≠ Pharmacokinetics | |
|---|---|
| Absorption can be delayed or prolonged | Elimination half-life can be increased |




Roberts DM, 2007.

# Self Assessment Question 1

MM is a 30 year old female brought into the emergency department after ingesting 30 tablets of her amlodipine 10 mg refill four hours ago. Upon confirmation, she did not co-ingest other substances. During provider's exam, she becomes bradycardic and hypotensive. Poison Control Center is consulted, a peripheral IV line is placed, and the provider is requesting therapy recommendations. What initial therapies would you start with? (**SELECT ALL THAT APPLY**)

A. Activated charcoal
B. Calcium gluconate
C. Glucagon
D. Norepinephrine

# Self Assessment Question 1

MM is a 30 year old female brought into the emergency department after ingesting 30 tablets of her amlodipine 10 mg refill four hours ago. Upon confirmation, she did not co-ingest other substances. During provider's exam, she becomes bradycardic and hypotensive. Poison Control Center is consulted, a peripheral IV line is placed, and the provider is requesting therapy recommendations. What initial therapies would you start with? (**SELECT ALL THAT APPLY**)

A. Activated charcoal
**B. Calcium gluconate**
C. Glucagon
**D. Norepinephrine**

# Therapy Management

- Activated charcoal
- **Calcium salts**
- Atropine
- Crystalloid bolus
- Vasopressors
- **Glucagon**
- **High-dose insulin euglycemic therapy**
- Lipid emulsion therapy
- VA-ECMO

# Calcium Salts

- Improves myocardial contractility and blood pressure in calcium channel blocker toxicity

## Calcium Gluconate

- Dose
  - Bolus: 3-6 g IV over 10 minutes
    - Repeat every 10 minutes
  - Infusion: 60-120 mg/kg/hr

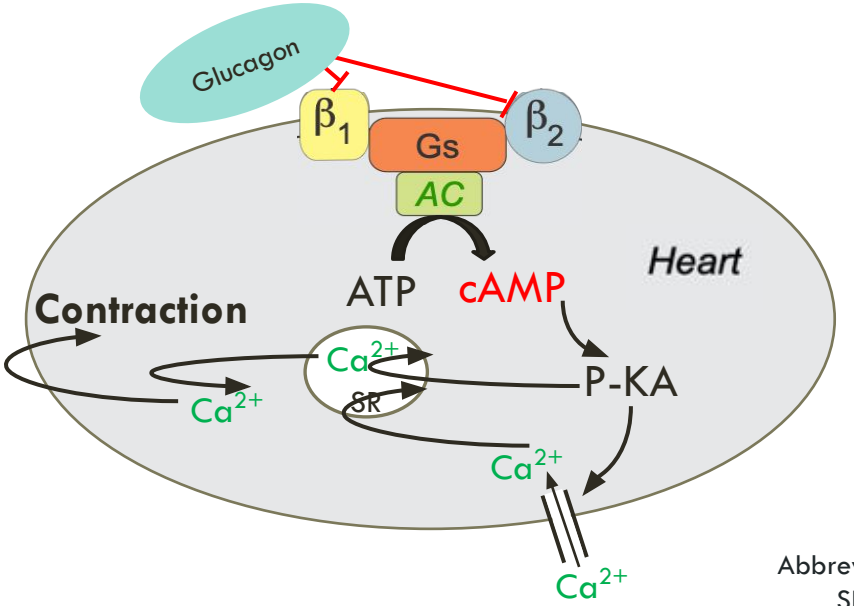
## Calcium Chloride

- Dose
  - Bolus: 1-3 g IV over 10 minutes
    - Repeat every 10 minutes
  - Infusion: 20-40 mg/kg/hr

St-Onge M, 2017.

# Glucagon

- Increases cyclic AMP at the SA and AV nodes to increase heart rate, cardiac output, and reverse AV nodal conduction blocks

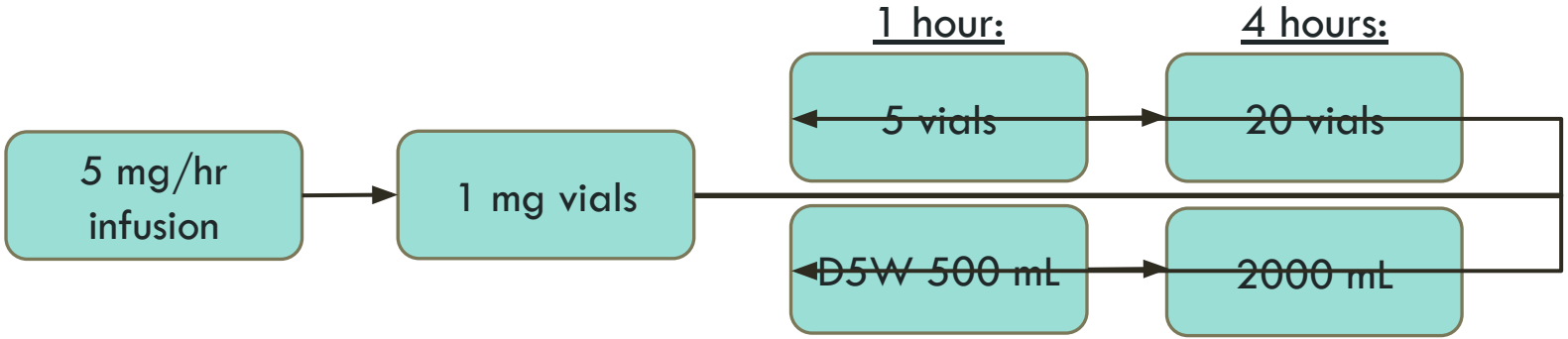



Abbreviations: P-KA, protein kinase; SR, sarcoplasmic reticulum

Shepherd G, 2005.
St-Onge M, 2017.

# Glucagon

- Dose
  - 3-10 mg IV push followed by 3-5 mg/hr infusion if responsive to IV push
- Adverse effects and operational considerations
  - Nausea/vomiting
  - Diminished hospital supply of glucagon




Bailey B, 2003.
Kusumoto FM, 2019.

# High-Dose Insulin Euglycemic Therapy

- Insulin in combination with glucose promotes carbohydrate metabolism by increasing myocardial glucose uptake, enhances inotropic function, and increases cardiac output
- Standard insulin infusions could result in fluid overload



Engebretsen KM, 2011.
St-Onge M, 2017.

# High-Dose Insulin Euglycemic Therapy

## Insulin

- Concentrated
- Dose
  - Bolus: 1 unit/kg IV push
  - Infusion: 1 unit/kg/hr
    - Titrate up to 10 units/kg/hr

## Dextrose

- Concentrated
- Dose
  - Bolus: 25 g if BG <250 mg/dL
  - Infusion: 0.5 g/kg/hr
    - Titrate up to 3 g/kg/hr

## Monitoring Parameters

- Blood pressure
- Blood glucose
- Serum Potassium

Engebretsen KM, 2011.
St-Onge M, 2017.

# CASE REPORTS

## Insulin-Glucose as Adjunctive Therapy for Severe Calcium Channel Antagonist Poisoning

Tony H. Yuan; William P. Kerns II; Christian A. Tomaszewski; Marsha D. Ford; Jeffrey A. Kline

*Carolinas Medical Center, Charlotte, North Carolina*

**ABSTRACT**

**Case Report: This case series documents the clinical courses of 4 patients after verapamil overdose and 1 patient after amlodipine-atenolol overdose. All subjects had hypodynamic circulatory shock (hypotension, bradycardia, and acidosis) that was not adequately responsive to conventional treatment. After initiation of insulin-dextrose infusion, the hemodynamic status of all 5 patients stabilized and all patients survived. Pl**

- Case 1:
  - Insulin 10 units bolus, 30 units/hr infusion
    - Highest insulin dose: 0.3 units/kg/hr
  - Dextrose 25 g bolus, D50 15 g/hr infusion
- Case 2:
  - Insulin 10 units bolus, 4 units/hr infusion
    - Highest insulin dose: 0.1 units/kg/hr
  - Dextrose 25 g bolus, D50 8 g/hr infusion
- Case 3:
  - Insulin 10 units bolus, 12 units/hr infusion
    - Highest insulin dose: 0.5 units/kg/hr
  - Dextrose 25 g bolus, D10 6 g/hr infusion
- Case 4:
  - Insulin 20 units bolus, 35 units/hr infusion
    - Highest insulin dose: 1 unit/kg/hr
  - Dextrose 25 g bolus, 5 g/hr infusion
- Case 5:
  - Insulin 20 units bolus, 35 units/hr infusion
    - Highest insulin dose: 0.5 units/kg/hr
  - Dextrose 25 g bolus, 7.5 g/hr infusion

Yuan TH, 1999.

Circulation

AHA FOCUSED UPDATE

# 2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

*Endorsed by the American Academy of Pediatrics*

Eric J. Lavonas, MD, MS, Chair; Peter D. Akpunonu, MD; Ann M. Arens, MD; Kavita M. Babu, MD; Dazhe Cao, MD; Robert S. Hoffman, MD; Christopher O. Hoyte, MD, MBA; Maryann E. Mazer-Amirshahi, PharmD, MD, MPH, PhD; Andrew Stolbach, MD, MPH; Maude St-Onge, MD, PhD; Trevonne M. Thompson, MD; George Sam Wang, MD; Amber V. Hoover, RN, MSN; Ian R. Drennan, ACP, PhD, Vice Chair; on behalf of the American Heart Association

Lavonas EJ, 2023.

# Operational Considerations

- Medication supply
  - Medication concentrations
  - Medication availability
- Duration of therapy for each patient may vary
  - Continued therapies with plan to order more supply
  - Assess rate changes and frequency of new infusion bag needed
  - Plan to taper therapy

# Self-Assessment Question 2

MM is a 30 year old female brought into the emergency department after ingesting 30 tablets of her amlodipine 10 mg refill four hours ago. Upon confirmation, she did not co-ingest other substances. During provider's exam, she becomes bradycardic and hypotensive. Poison Control Center is consulted, a peripheral IV line is placed, and she receives calcium gluconate, a crystalloid fluid bolus, and is started on norepinephrine, while the provider orders high dose insulin. What is the initial dose of insulin?

A. Insulin 0.1 unit/kg/hr infusion
B. Insulin 10 units/kg/hr infusion
C. Insulin 0.1 unit/kg IV bolus + 0.1 unit/kg/hr infusion
D. Insulin 1 unit/kg IV bolus + 1 unit/kg/hr infusion

# Self-Assessment Question 2

MM is a 30 year old female brought into the emergency department after ingesting 30 tablets of her amlodipine 10 mg refill four hours ago. Upon confirmation, she did not co-ingest other substances. During provider's exam, she becomes bradycardic and hypotensive. Poison Control Center is consulted, a peripheral IV line is placed, and she receives calcium gluconate, a crystalloid fluid bolus, and is started on norepinephrine, while the provider orders high dose insulin. What is the initial dose of insulin?

A. Insulin 0.1 unit/kg/hr infusion
B. Insulin 10 units/kg/hr infusion
C. Insulin 0.1 unit/kg IV bolus + 0.1 unit/kg/hr infusion
**D. Insulin 1 unit/kg IV bolus + 1 unit/kg/hr infusion**

# Summary

- Beta blocker and calcium channel blocker toxicity are common toxicities seen in the emergency department and can result in high morbidity and mortality
- Hallmark signs of toxicity include hypotension and bradycardia
- Early identification and management can improve patient outcomes
- Use of concentrated insulin and dextrose infusions can reduce the risk of fluid overload and hypoglycemic events
- Operational and logistical challenges must be addressed promptly to ensure therapy is administered to the patient timely

# References


- Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. *Journal of Toxicology*. 2003;41(5):595-602.
- Engebretsen KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clinical Toxicology*. 2011; 49:277-283.
- Gummin DD, Mowry JB, Beuhler MC, et al. 2020 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th annual report. *Clinical Toxicology*. 2021;59(12):1282-1501.
- Hoffman RS, Howland MA, Lewin NA, et al. Initial evaluation of the patient: vital signs and toxic syndromes. *Goldfrank's Toxicologic Emergencies, 10e. McGraw Hill*. 2015. Available at: https://accessemergencymedicine.mhmedical.com/content.aspx?bookid=1163&sectionid=64552562.
- Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/.American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. *J Am Call Cardiol*. 2019;74(7):e51-e156.
- Lashari BH, Minalyan A, Khan W, et al. The use of high-dose insulin infusion and lipid emulsion therapy in concurrent beta-blocker and calcium channel blocker overdose. *Cureus*. 2018;10(11)e3534.
- Lavonas EJ, Akpunonu PD, Arens AM, et al. 2023 American Heart Association focused update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2023;148:e00-e00.
- Roberts DM, Buckley NA. Pharmacokinetic considerations in clinical toxicology. *Clinical Pharmacokinetics*. 2007;46:897-939.
- Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium channel blocker overdose. *Ann Pharmacother*. 2005;39(5):923-930.
- St-Onge, M, Anseeuw K, Cantrell FL, et al. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. *Crit Care Med*. 2017;45(3):e306-e315.
- Yuan TH, Kerns II WP, Tomaszewski CA, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *Clinical Toxicology*. 1999;37(4):463-474.

We are called to make a healthy difference in people's lives.

*Bugs and Drugs: NDSHP Clinical Pearls*

# The Use of Prolonged-Infusion Beta-Lactam Antibiotics

Riley Steenhoek, PharmD

Acute Care Pharmacist

Essentia Health

# Disclosures

I have no relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

*At the completion of this activity, the participant will be able to:*

*1. Identify the potential benefits associated with probiotics in reducing antibiotic associated diarrhea and C. difficile.*

*2. Outline how to incorporate a pharmacist-managed probiotic protocol.*

*3. Determine the appropriate treatment for an ESBL and AmpC bacteria.*

*4. Compare and contrast the differences between how to classify a bacteria as ESBL or AmpC.*

*5. Examine treatment options available for beta blocker and calcium channel blocker toxicity.*

***6. Discuss the difference between time-dependent and concentration dependent antibiotics.***

***7. Review lengths of infusion rates to determine appropriate length type of infusion.***

***8. Classify patient population with a consensus recommendation for prolonged infusions vs. short infusions of beta-lactams.***

# Background

SPECIAL ARTICLE

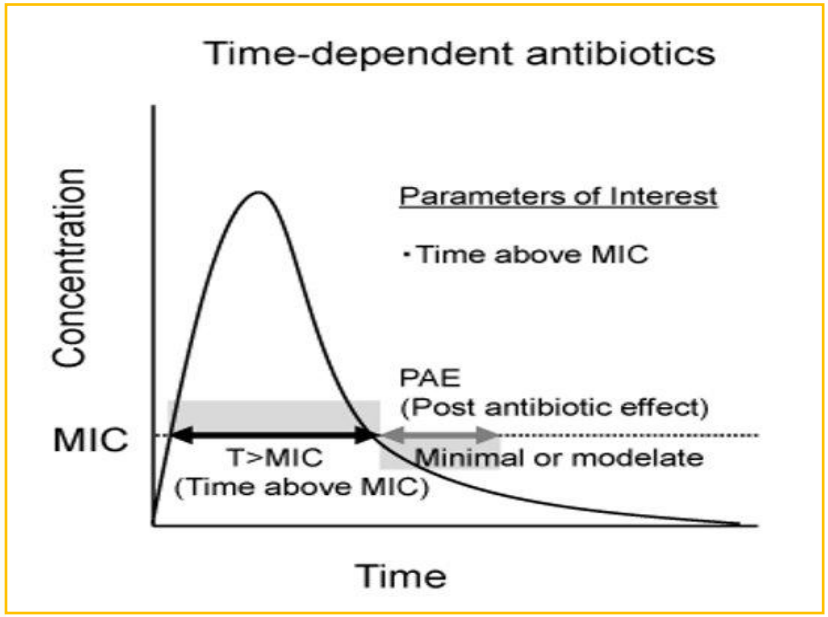
## International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists

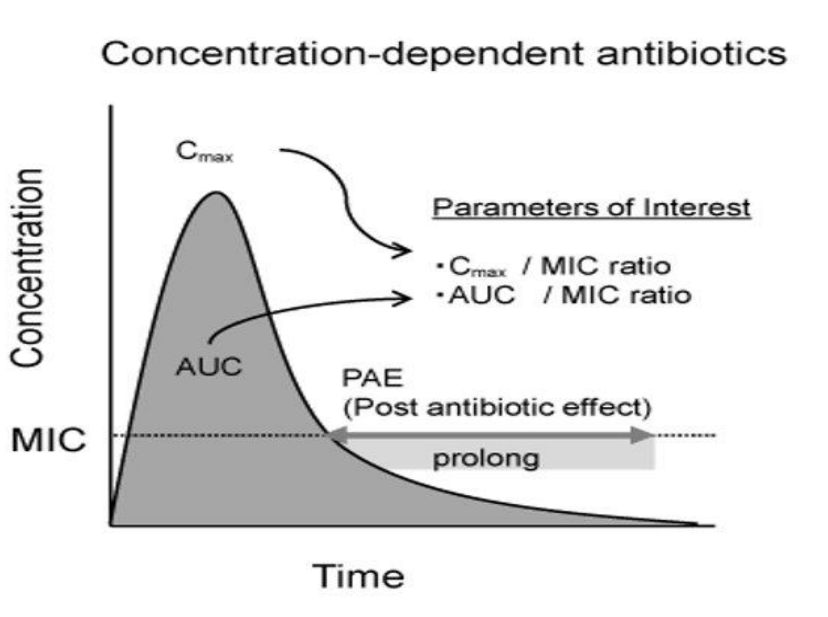
Lisa T. Hong[1] | Kevin J. Downes[2] | Alireza FakhriRavari[1] | Jacinda C. Abdul-Mutakabbir[1,3] | Joseph L. Kuti[4] | Sarah Jorgensen[5] | David C. Young[6] | Mohammad H. Alshaer[7] | Matteo Bassetti[8] | Robert A. Bonomo[9,10] | Mark Gilchrist[11] | Soo Min Jang[1] | Thomas Lodise[12] | Jason A. Roberts[13,14,15,16] | Thomas Tängdén[17] | Athena Zuppa[2] | Marc H. Scheetz[18,19]



Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics

# Background






Source: https://www.omicsonline.org/articles-images/JBB-S2-002-g002.html

Eagle H, Fleischman R, Levy M. "Continuous" vs. "discontinuous" therapy with penicillin; the effect of the interval between injections on therapeutic efficacy

# Definitions

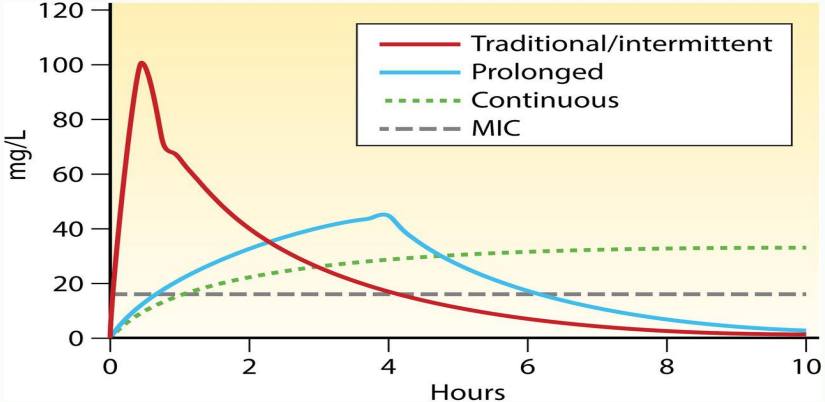
- Prolonged Infusion (PI) ≥ 3 hours
- Prolonged Infusion = Extended Infusion (EI) and Continuous Infusion (CI)
  - Distinguished as appropriate moving forward
- Short Infusion (SI) ≤ 1 hour
  - Excluding intravenous (IV) push or bolus unless expressed
- Infusions between 1 hour to 3 hours are not classified
- Time the free concentration of the drug remains above the MIC during the dosing interval ($fT_{>MIC}$)



Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics

# Prolonged Infusion vs. Short Infusion

- In Vitro & Animal Data
  - Predominately studied with gram-negative bacteria
  - Equivalent or better bacterial killing for PI compared with SI – Attributed to greater $fT_{>MIC}$






Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics
Grupper, M., Kuti, J. L., & Nicolau, D. P. (2016). Continuous and prolonged intravenous β-lactam dosing: Implications for the clinical laboratory

# Prolonged Infusion vs. Short Infusion

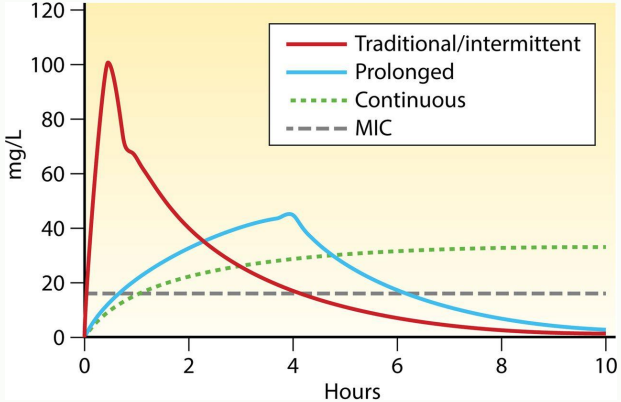
- Conesus on PI vs. SI β- lactams in…
  - Severely ill adult patients:
    - **PI is recommended over SI** to reduce mortality or increase clinical cure
  - Non-severely ill adult patients:
    - No recommendation for PI over SI to reduce mortality or increase clinical cure
  - Safety…
    - No recommendation for PI over SI for safety advantage and reduce adverse effects
  - Special Populations…
    - No recommendation for PI over SI to improve efficacy of β- lactams (Obesity, neonates, pediatrics)



Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics

# Loading Dose

- Consensus Recommendation:
  - Loading dose in continuous infusions to improve clinical success
  - No recommendation in extended infusions






Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics Grupper, M., Kuti, J. L., & Nicolau, D. P. (2016). Continuous and prolonged intravenous β-lactam dosing: Implications for the clinical laboratory

# Targets & Resistance Suppression

- Preclinical Targets:
  - Short Infusion (SI) and 4-H Extended Infusion (EI)
    - Reduction in CFU = 40-70% $fT_{>MIC}$
  - Continuous Infusions (CI)
    - Reduction in CFU = 100% $fT_{>MIC}$ with concentrations > 4-8x free drug over steady-state concentration
- Resistance Suppression
-
  - Prolonged infusion and by exceeding MIC by 4-6x may minimize resistance
    - No absolute target guarantees suppression of resistance



Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics

# Therapeutic Drug Monitoring (TDM)?

- No current recommendation on routine TDM
  - Personalized dosing may be considered
- If TDM is performed:
  - Minimum plasma exposures of at least 50%–70% $fT_{>MIC}$ be targeted for β- lactams when administered as SI and EI
  - β- lactams administered as CI, we suggest 100% $fT_{>MIC}$ with concentrations at least four times the MIC



Source: Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics

# Stability Concerns

| Antibiotic | Syringe (48 mL, 25 °C), Polyolefin Bags * (100 mL, 25 °C) | | | Diffuser (37 °C) | | |
|---|---|---|---|---|---|---|
| | Amount (g) (Concentration) | Solvent | Stability (Hours) | Amount (g) (Concentration) | Solvent | Stability (Hours) |
| Amoxicillin * | 2 g (100 mL) (20 mg/mL) | NS ** | 12 h | Unrealized in elastomeric device | | |
| Aztreonam | 6 g (125 mg/mL) | NS-D5W *** | 48 h | 6 g (120 mL) (50 mg/mL) | NS-D5W | 48 h |
| Cefazolin | 6 g (125 mg/mL) | NS-D5W | 24 h | 6 g (120 mL) (50 mg/mL) | NS-D5W | Precipitate formation during the pre-study |
| Cefepime | 6 g (125 mg/mL) | NS-D5W | 24 h | 6 g (120 mL) (50 mg/mL) | NS | Visual modification after 6 h at 37 °C |
| Cefiderocol | 3 g (62.5 mg/mL) | NS-D5W | 24 h | 6 g (240 mL) (25 mg/mL) | NS- D5W | 6 h |
| Cefotaxime | 4 g–6 g (83.3–125 mg/mL) | NS-D5W | 6 h | 6 g (240 mL) (25 mg/mL) | NS-D5W | Colour change after 6 h during the pre-study |
| Cefoxitin | 6 g (125 mg/mL) | D5W | 12 h | 6 g (240 mL) (25 mg/mL) | NS-D5W | Instability during the pre-study |
| Ceftazidime | 6 g (125 mg/mL) | NS<br>D5W | 24 h<br>8 h | 3 g (120 mL) (25 mg/mL) | NS-D5W | 8 h |
| Ceftazidime/ Avibactam | 6/1.5 g (125/31.25 mg/mL) | NS-D5W | 24 h | 3/0.75 g (120 mL) (25/6.25 mg/mL) | NS<br>D5W | 12 h<br>Unstable |
| Ceftozolane/ Tazobactam | 3/1.5 g (62.5/31.25 mg/mL) | NS-D5W | 48 h | 3/1.5 g (120 mL) (25/12.5 mg/mL) | NS<br>D5W | 12 h<br>8 h |
| Cloxacillin | 12 g (250 mg/mL) | SWFI **** | 24 h | 6–12 g (120 mL) (50–100 mg/mL) | NS-D5W | Precipitate formation during the pre-study |
| | 6 g (125 mg/mL) | NS-D5W | 24 h | | | |
| Meropenem | 2 g (41.7 mg/mL) | NS<br>D5W | 8 h<br>4 h | Unrealized in elastomeric device | | |
| Piperacillin | 6 g (125 mg/mL) | NS<br>D5W | 24 h<br>48 h | 16 g (240 mL) (66.7 mg/mL) | NS-D5W | Instability during the pre-study |
| Piperacillin / Tazobactam | 6/0.75 g (125/15.6 mg/mL) | NS-D5W | 48 h | 16/2 g (240 mL) (66.7/8.3 mg/mL) | NS<br>D5W | 8 h<br>24 h |
| Temocillin | Unrealized | | | 6 g (240 mL) (25 mg/mL) | NS<br>D5W | 24 h<br>Unstable |
| Vancomycin | 3 g (62.5 mg/mL) | D5W | 48 h | 4.5 g (120 mL) (37.5 mg/mL) | NS-D5W | 48 h |
| | 4 g (83.3 mg/mL) | D5W | 48 h | | | |

Stability must be considered on a drug-drug basis



Loeuille G, D'Huart E, Vigneron J, Nisse Y-E, Beiler B, Polo C, Ayari G, Sacrez M, Demoré B, Charmillon A. Stability Studies of 16 Antibiotics for Continuous Infusion in Intensive Care Units and for Performing Outpatient Parenteral Antimicrobial Therapy

# References


1. https://www.omicsonline.org/articles-images/JBB-S2-002-g002.html
2. Hong, LT, Downes, KJ, FakhriRavari, A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2023; 43: 740-777. doi:10.1002/phar.2842
3. Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. Clin Infect Dis. 2007;45(Suppl 1):S89-S95.
4. Grupper M, Kuti JL, Nicolau DP. Continuous and prolonged intra-venous beta-lactam dosing: implications for the clinical laboratory. Clin Microbiol Rev. 2016;29:759-772.
5. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis. 1998;27:10-22.
6. Eagle H, Fleischman R, Levy M. “Continuous” vs. “discontinuous” therapy with penicillin; the effect of the interval between injections on therapeutic efficacy. N Engl J Med. 1953;248:481-488.
7. Vinks AA, Brimicombe RW, Heijerman HG, Bakker W. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. J Antimicrob Chemother. 1997;40:125-133.
8. Yusuf E, Spapen H, Pierard D. Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and systematic review. J Crit Care. 2014;29:1089-1095.
9. Grupper, M., Kuti, J. L., & Nicolau, D. P. (2016). Continuous and prolonged intravenous β-lactam dosing: Implications for the clinical laboratory. Clinical Microbiology Reviews, 29(4), 759–772. https://doi.org/10.1128/cmr.00022-16
10. Loeuille G, D’Huart E, Vigneron J, Nisse Y-E, Beiler B, Polo C, Ayari G, Sacrez M, Demoré B, Charmillon A. Stability Studies of 16 Antibiotics for Continuous Infusion in Intensive Care Units and for Performing Outpatient Parenteral Antimicrobial Therapy. Antibiotics. 2022; 11(4):458. https://doi.org/10.3390/antibiotics11040458

We are called to make a healthy difference in people's lives.

# Thank You

Questions?

Essentia Health

We are called to make a healthy difference in people's lives.

*Bugs and Drugs: NDSHP Clinical Pearls*

# TREATMENT OF RESISTANT GRAM-NEGATIVE INFECTIONS

Tony Maanum, PharmD

PGY-1 Acute Care Pharmacy Resident

Essentia Health - Fargo

Essentia Health

# Disclosure

Tony Maanum has no relevant financial relationships with ineligible companies to disclose. None of the planners, faculty, and others in control of content of this educational activity have relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

*At the completion of this activity, the participant will be able to:*

*1. Identify the potential benefits associated with probiotics in reducing antibiotic associated diarrhea and C.difficile.*

*2. Outline how to incorporate a pharmacist-managed probiotic protocol.*

***3. Determine the appropriate treatment for an ESBL and AmpC bacteria.***

***4. Compare and contrast the differences between how to classify a bacteria as ESBL or AmpC.***

*5. Examine treatment options available for beta blocker and calcium channel blocker toxicity.*

*6. Discuss the difference between time-dependent and concentration dependent antibiotics.*

*7. Review lengths of infusion rates to determine appropriate length type of infusion.*

*8. Classify patient population with a consensus recommendation for prolonged infusions vs. short infusions of beta-lactams.*

# Abbreviations

- AMS – antimicrobial stewardship
- CDC – Center for Disease Control
- CFU – colony forming units
- CRAB – carbapenem-resistant Acinetobacter baumannii
- CRE – carbapenem-resistant enterobacterales
- CTX-M – cefotaximase-Munich
- C-UTI – complicated urinary tract infection
- DOT – duration of therapy
- DTR – difficult to treat resistance
- ESBL - extended spectrum β-lactamase enterobacterales
- GU – genitourinary
- ICP – intracranial pressure
- IDSA – Infectious Disease Society of America
- MIC – minimum inhibitory concentration
- Pip/Tazo - piperacillin-tazobactam
- RBC – red blood cells
- SMX/TMP - sulfamethoxazole-trimethoprim
- UA – urinary analysis
- UTI – urinary tract infection
- WBC – white blood cells

We are called to make a healthy difference in people's lives.

# Extended Spectrum β-Lactamase Producing Enterobacterales

## (ESBL)

Essentia Health

# Most Common ESBL Producing Bacteria

- Escherichia coli
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Proteus mirabilis
- Any gram-negative bacteria



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Cystitis Treatment

| | |
|---|---|
| Primary therapy | • Nitrofurantoin or SMX/TMP |
| Secondary therapy | • Levofloxacin, ciprofloxacin, carbapenems |
| Alternative therapy | • Single-dose aminoglycoside or fosfomycin |



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Fosfomycin Pearl

- Fosfomycin should only be used in ESBL E. coli
- Most other bacteria carry a fosA hydrolase gene
- This enzyme will confer fosfomycin resistance to the bacteria by conjugating glutathione to fosfomycin

**Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal *fosA* Gene**

**The Role of *fosA* in Challenges with Fosfomycin Susceptibility Testing of Multispecies Klebsiella pneumoniae Carbapenemase-Producing Clinical Isolates**



Ito R, Mustapha MM, Tomich AD, Callaghan JD, McElheny CL, Mettus RT, Shanks RMQ, Sluis-Cremer N, Doi Y. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. mBio. 2017 Aug 29;8(4):e00749-17. doi: 10.1128/mBio.00749-17. PMID: 28851843; PMCID: PMC5574708.
Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Pyelonephritis Treatment

| | |
|---|---|
| Primary treatment | • SMX/TMP, levofloxacin, ciprofloxacin |
| Secondary therapy | • Ertapenem, meropenem, imipenem-cilastatin |
| Alternative therapy | • Full course aminoglycosides |



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# ESBL Outside the GU System

| | |
|---|---|
| Preferred treatment | • Meropenem, imipenem-cilastatin, ertapenem |
| Step-down therapy | • SMX/TMP, levofloxacin, ciprofloxacin |



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Ertapenem Pearl

- Ertapenem should be used with caution in patients with hypoalbuminemia or who are critically ill
- Ertapenem is extremely protein bound which greatly increases its half-life
- This study shows that patients had a 5-times higher risk of mortality when using ertapenem compared to meropenem or imipenem/cilistatin

**Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study**



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.
Zusman O, Farbman L, Tredler Z, Daitch V, Lador A, Leibovici L, Paul M. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect. 2015 Jan;21(1):54-8. doi: 10.1016/j.cmi.2014.08.003. Epub 2014 Oct 12. PMID: 25636928.

# Piperacillin-Tazobactam – Merino Trial

- Compared Pip/Tazo to meropenem for bloodstream infections
- Differences between susceptibilities and clinical results
- Not recommended for use over other agents

**Effect of Piperacillin–Tazobactam vs Meropenem on 30–Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial**



Harris PNA, Tambyah PA, Lye DC, Mo Y, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18;321(23):2370. PMID: 30208454; PMCID: PMC6143100
Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of

# Cefepime and Cephamycins

## Cefepime

- May show susceptibilities but not recommended for use
- Studies have shown high failure rates
- More data may be needed to assess true efficacy

## Cephamycins

- Not enough data
- Many cephamycins being studies are not available in the US
- **Cefoxitin and cefotetan are the most common**
- Not recommended



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# β-Lactam-β-Lactamase Inhibitor Combinations and Cefiderocol

- Reserved for carbapenem resistant organisms
  - Meropenem-vaborbactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol
- Ceftolozone-tazobactam should be avoided as treatment



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Review

- Bacteria:
  E. coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis
- Susceptibility:
  - Ceftriaxone MIC > 2
  - Multi-resistance
- Treatment:
  - Cystitis - Nitrofurantoin or SMX/TMP
  - Pyelonephritis - SMX/TMP, levofloxacin, ciprofloxacin
  - Other sources - Meropenem, imipenem-cilastatin, ertapenem



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

We are called to make a healthy difference in people's lives.

# AmpC
# β-Lactamase Producing Enterobacterales
# (AmpC)

Essentia Health

# Sensitivities

Inducible AmpC may initially appear susceptible to ceftriaxone, cefotaxime, and ceftazidime

Exposure to these will start AmpC production which will cause them to lose susceptibility



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Antibiotics and Induction

| Strong Inducers | Retained Activity |
| --- | --- |
| • Aminopenicillins<br>• 1st generation cephalosporins<br>• Cephamycins<br>• Carbapenems | • Cefepime<br>• Carbapenems |



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Most Common AmpC Producing Bacteria

HECK-Yes

- **H**afnia alvei
- **E**nterobacter cloacae
- **C**itrobacter freundii
- **K**lebsiella aerogenes
- **YE**r**S**inia enterocolitica

Less commonly seen

- Serratia marcescens
- Morganella morganii
- Providencia spp.



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Cefepime

- Retained activity against AmpC
- Preferred treatment for AmpC
- Caution with MIC > 4



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Ceftriaxone, Ceftazidime, Cefotaxime

- Moderate AmpC inducers
- Do not retain activity against AmpC hydrolysis
- Not recommended for treatment
- Do not use against HECK-Yes bacteria



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Piperacillin-Tazobactam

- Not recommended
- Conflicting study data
- Poor in vitro results
- More data is needed



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# β-Lactam-β-Lactamase Inhibitor Combinations and Cefiderocol

- Reserved for carbapenem resistant organisms
  - Meropenem-vaborbactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol
- Ceftolozone-tazobactam should be avoided as treatment



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Non-β-Lactam Therapies

| | |
|---|---|
| Nitrofurantoin | • Uncomplicated cystitis |
| SMX/TMP | • Uncomplicated cystitis, pyelonephritis, other invasive infections |
| Fluoroquinolones | • Uncomplicated cystitis, pyelonephritis, other invasive infections |
| Aminoglycosides | • Uncomplicated cystitis, pyelonephritis |



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Review

- Bacteria:
  - Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes
- Susceptibility:
  - Ceftriaxone may show susceptibility
  - Cefepime MIC > 4 = Caution
- Treatment:
  - Cefepime
  - Nitrofurantoin, SMX/TMP, Fluoroquinolones
  - Carbapenems



Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

# Patient Case #1

HPI: TR is a 64-year-old male who presents with flank pain and urinary frequency. His urinary analysis and culture are shown below

**URINALYSIS, REFLEX TO CULTURE**
**Collection Time: 08/30/23 11:27 PM**
**Specimen: Urine CVMS**

| Result | Value | Ref Range |
|---|---|---|
| Urine Color | Yellow | Straw, Yellow, Amber |
| Urine Appearance | Turbid (A) | Clear |
| Urine Specific Gravity | 1.019 | 1.003 - 1.035 |
| Urine pH | 5.0 | 5.0 - 8.0 |
| Urine Glucose | Negative | Negative |
| Urine Ketones | Negative | Negative |
| Urine Protein | >=500 (A) | Negative, Trace mg/dL |
| Urine Nitrites | Positive (A) | Negative |
| Urine Leukocyte Esterase | Large (A) | Negative |
| Urine WBC's | >182 (A) | 0 - 8 /HPF |
| Urine RBC's | >182 (A) | 0 - 3 /HPF |
| Urine Squamous Epithelial Cells | None Seen | /HPF |
| Urine Bacteria | Occasional (A) | None Seen /HPF |

Specimen: Urine
Organism: > 100,000 CFU/mL *E. coli*

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Nitrofurantoin | <32 | Sensitive |
| SMX/TMP | <2/38 | Sensitive |
| Ceftriaxone | >2 | Resistant |
| Cefepime | <2 | Sensitive |
| Pip/Tazo | <16/4 | Sensitive |
| Meropenem | <1 | Sensitive |

ESBL Resistance CTX-M Gene — Detected !

# Question #1

What would be the most appropriate choice of antibiotic for TR?

1. Pip/Tazo
2. Cefepime
3. Nitrofurantoin
4. Meropenem
5. SMX/TMP

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Nitrofurantoin | <16 | Sensitive |
| SMX/TMP | <2/38 | Sensitive |
| Ceftriaxone | >2 | Resistant |
| Cefepime | <2 | Sensitive |
| Pip/Tazo | <8/4 | Sensitive |
| Meropenem | <1 | Sensitive |

ESBL Resistance CTX-M Gene Detected !

# Question #1 Rationale

ESBL

## Pyelonephritis Treatment

| | |
|---|---|
| Primary treatment | • SMX/TMP, levofloxacin, ciprofloxacin |
| Secondary therapy | • Ertapenem, meropenem, imipenem-cilastatin |
| Alternative therapy | • Full course aminoglycosides |

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Nitrofurantoin | <16 | Sensitive |
| SMX/TMP | <2/38 | Sensitive |
| Ceftriaxone | >2 | Resistant |
| Cefepime | <2 | Sensitive |
| Pip/Tazo | <8/4 | Sensitive |
| Meropenem | <1 | Sensitive |

Organism: > 100,000 CFU/mL *E. coli*

ESBL Resistance CTX-M Gene Detected !

# Patient Case #2

- HPI: DM is a 52-year-old female who has been in the hospital for 7 days. Over the past 6 hours she has become lethargic and pale. Her blood pressure has dropped to 72/54 and her WBC has increased to 17.2. Blood cultures were ordered, and the results are shown below

Blood
Culture: Citrobacter freundii

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Ceftriaxone | <2 | Sensitive |
| Cefepime | <2 | Sensitive |
| Meropenem | <1 | Sensitive |
| Gentamycin | <2 | Sensitive |

# Question #2

What would be the most appropriate choice of antibiotic for DM?

1. Ceftriaxone
2. Meropenem
3. Cefepime
4. Gentamycin
5. Amoxicillin/Clavulanate

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Ceftriaxone | <2 | Sensitive |
| Cefepime | <2 | Sensitive |
| Meropenem | <1 | Sensitive |
| Gentamycin | <2 | Sensitive |

Blood Culture: *Citrobacter freundii*

# Question #2 Rationale

AmpC

## Cefepime

- Retained activity against AmpC
- Preferred treatment for AmpC
- Caution with MIC>4

AmpC

## Ceftriaxone, Ceftazidime, Cefotaxime

- Moderate AmpC inducers
- Do not retain activity against AmpC hydrolysis
- Not recommended for treatment even if it reports as sensitive
- Do not use against HECK-Yes bacteria

| Antimicrobial | MIC | Interpretive category |
|---|---|---|
| Ceftriaxone | <2 | Sensitive |
| Cefepime | <2 | Sensitive |
| Meropenem | <1 | Sensitive |
| Gentamycin | <2 | Sensitive |

Blood Culture: *Citrobacter freundii*

# Resources


- 2019 antibiotic resistance threats report. Centers for Disease Control and Prevention. November 23, 2021. Accessed August 20, 2023. https://www.cdc.gov/drugresistance/biggest-threats.html#extend.
- Bush K, Bradford PA. β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8):a025247. doi: 10.1101/cshperspect.a025247. PMID: 27329032; PMCID: PMC4968164.
- Elliott ZS, Barry KE, Cox HL, Stoesser N, Carroll J, Vegesana K, Kotay S, Sheppard AE, Wailan A, Crook DW, Parikh H, Mathers AJ. The Role of *fosA* in Challenges with Fosfomycin Susceptibility Testing of Multispecies Klebsiella pneumoniae Carbapenemase-Producing Clinical Isolates. J Clin Microbiol. 2019 Sep 24;57(10):e00634-19. doi: 10.1128/JCM.00634-19. PMID: 31340992; PMCID: PMC6760957.
- Harris PNA, Tambyah PA, Lye DC, Mo Y, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18;321(23):2370. PMID: 30208454; PMCID: PMC6143100.
- Ito R, Mustapha MM, Tomich AD, Callaghan JD, McElheny CL, Mettus RT, Shanks RMQ, Sluis-Cremer N, Doi Y. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal *fosA* Gene. mBio. 2017 Aug 29;8(4):e00749-17. doi: 10.1128/mBio.00749-17. PMID: 28851843; PMCID: PMC5574708.
- Meini, Simone & Tascini, Carlo & Cei, Marco & Sozio, Emanuela & Rossolini, Gian. (2019). AmpC β-lactamase-producing Enterobacterales: what a clinician should know. Infection. 47. 10.1007/s15010-019-01291-9.
- Olszańska, Dorota & Zórawski, Marcin & Hauschild, Tomasz & Wieczorek, Piotr & Sacha, Pawel & Tryniszewska, Elzbieta. (2008). Metallo-beta-lactamases of Pseudomonas aeruginosa--a novel mechanism resistance to beta-lactam antibiotics.. Folia Histochemica et Cytobiologica. 46. 10.5603/4440.
- Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America **2023**; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.
- Zusman O, Farbman L, Tredler Z, Daitch V, Lador A, Leibovici L, Paul M. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect. 2015 Jan;21(1):54-8. doi: 10.1016/j.cmi.2014.08.003. Epub 2014 Oct 12. PMID: 25636928.

We are called to make a healthy difference in people's lives.

# Thank you

tony.maanum@essentiahealth.org

Essentia Health

# CPE Instructions for:

## Bugs and Drugs: NDSHP Clinical Pearls

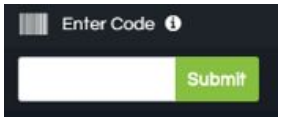
**1**

Redeem your credit online at **CEimpact.com**

*If this is the first time you have utilized the CEimpact Learning Management System (LMS) you will need to create an account.

**2**

From the **CEimpact.com** Homepage – enter the code provided in the 'Enter Code' box and click SUBMIT.




**3**

Complete the Exam & Evaluation as prompted; click SUBMIT to send your information to CPE Monitor. Follow instructions to access your CPE Statement of Credit on CPE Monitor or access your Certificate of Completion in MyCourses.

# Pharmacist Code: HxXZuq

**The deadline for obtaining your CPE Credit is 30 days from today.** The deadline is non-negotiable due to CPE Monitor reporting policies. For CME, access your certificate of completion in My Courses for this course.