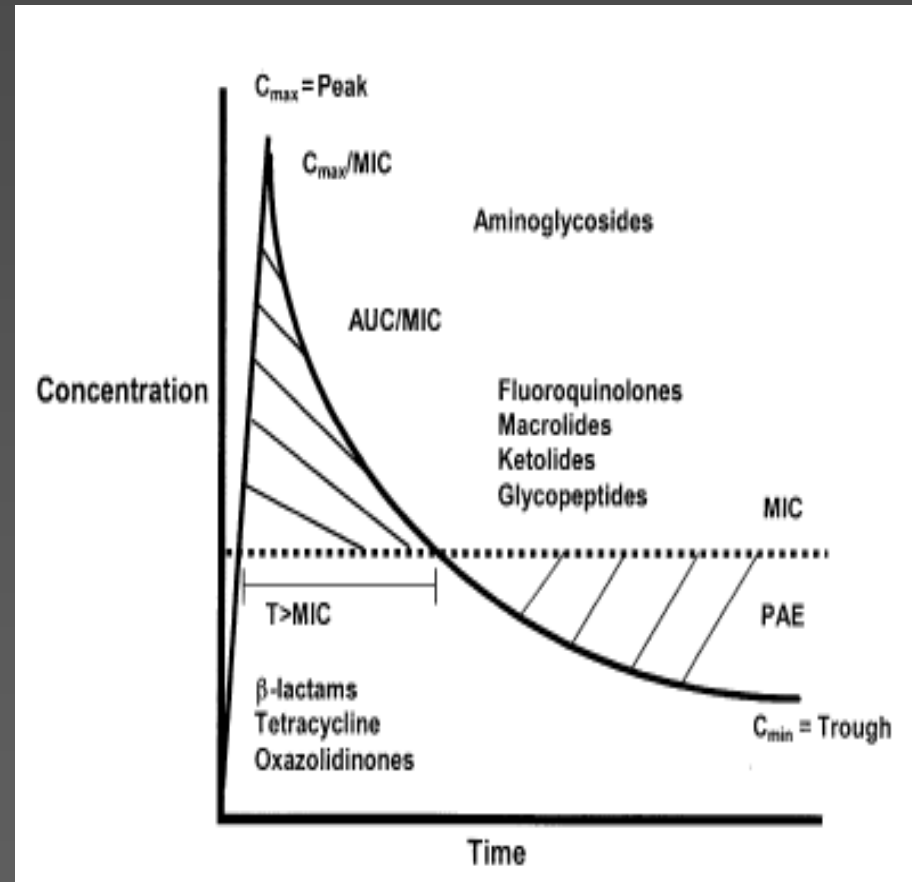


# Anti-Infective Dosing Protocols: Meropenem, Cefepime, and Piperacillin/tazobactam

# Background

The pharmacodynamic parameter that best correlates with optimal activity of  $\beta$ -lactams is the proportion of the dosing interval that the free drug concentration remains above the minimum inhibitory concentration (MIC) for the infecting organism – %fT>MIC (killing maximized at 4x MIC).



Rybak MJ. Am J Med 2006;119:S37-S44.  
Kollef MH Surgical Infections 2006;2:85-99.

# Pharmacodynamic Targets

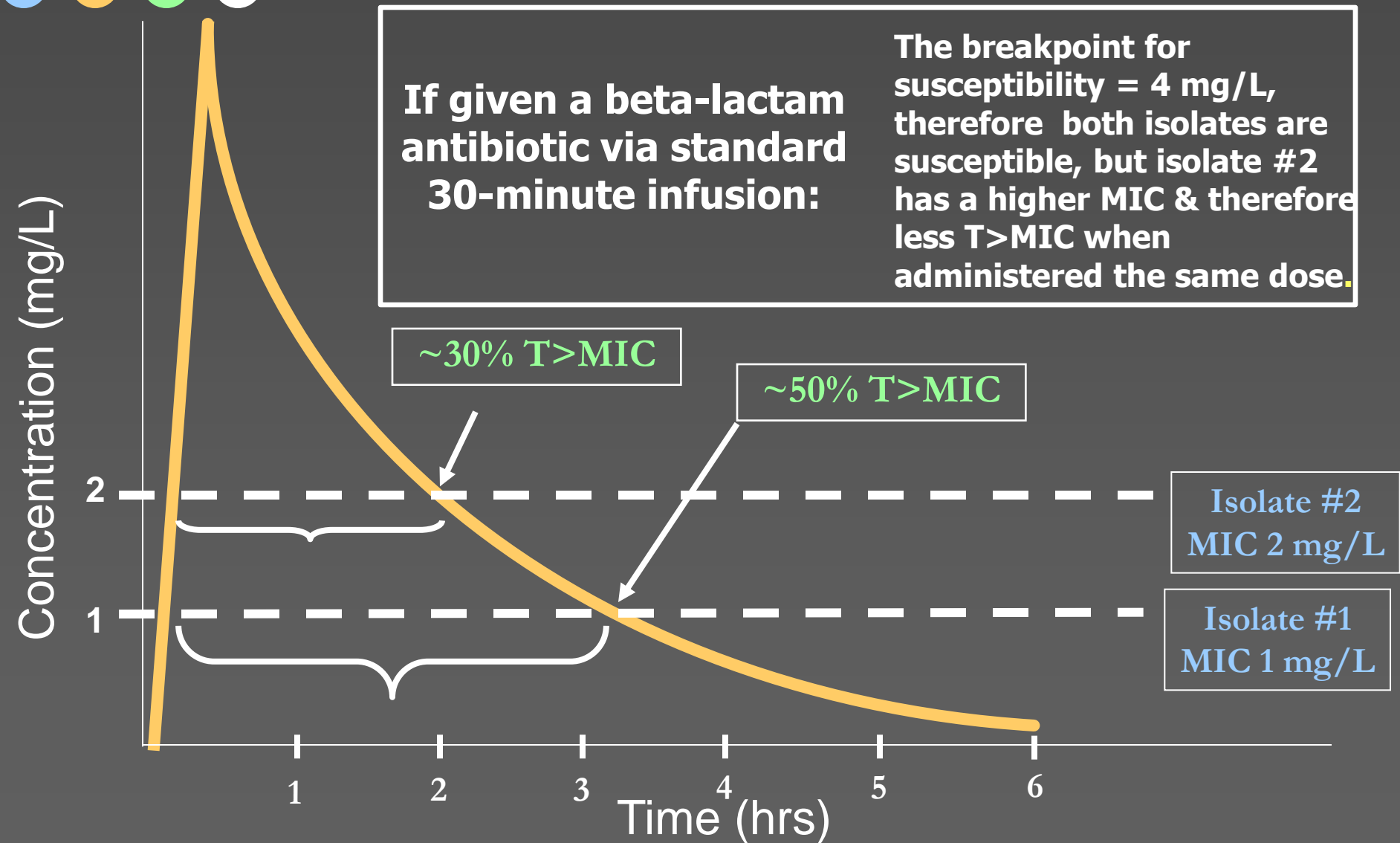
- The targets for %fT>MIC vary among the different sub-classes of  $\beta$ -lactams and organisms as illustrated below:

Pathogen	Carbapenems (%fT>MIC)	Penicillins (%fT>MIC)	Cephalosporins (%fT>MIC)
Gram-positive	20-30	30-40	40-50
Gram-negative	40-50	50-60	60-70

Ambrose PG, et al. Clin Infect Dis. 2007; 44: 79-86.

Craig WA. Clin Infect Dis. 1998; 26: 1-10; quiz 11-2.

# Impact of MIC value on Pharmacodynamic Targets



# Internal MIC Data

- A random selection of 30 blood isolates and 12 sputum isolates growing *Pseudomonas aeruginosa* were evaluated, and MICs were obtained via Sensititre susceptibility plates.

	Susceptible MIC (mg/L)	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)
Meropenem	≤ 1	≤ 1	4
Cefepime	≤ 8	8	16
Piperacillin/tazobactam	≤ 64	8	≥ 64

MIC50 = MIC needed to inhibit the growth of 50% of the isolates

MIC90 = MIC needed to inhibit the growth of 90% of the isolates



# Summary



- From the table, one can see that at the MIC needed to inhibit 90% of *P. aeruginosa* for all 3 drugs is at or above the breakpoint for susceptibility
- Therefore, it will be difficult to achieve adequate PK/PD targets for both cefepime and piperacillin/tazobactam



# How can we optimize %fT>MIC?



1. Give the drug more frequently (decrease the dosing interval)
2. Extend the infusion of the drug
3. Increase dose (less useful for agents with short half-lives)



# How can we optimize %fT>MIC?




1. Give the drug more frequently (decrease the dosing interval)
  - Meropenem
  - Cefepime
2. Extend the infusion of the drug
  - Piperacillin/Tazobactam





# Give the Drug More Frequently

- 
- Meropenem
    - Standard dose: 1g IV q8h
    - Dosage substitution: 500mg IV q6h
  - Cefepime
    - Standard dose: 2g IV q8h
    - Dosage substitution: 1g IV q6h

# Meropenem Target Attainment vs. *P. aeruginosa*

Regimen	MIC (mg/L)						
	0.25	0.5	1	2	4	8	16
1g q8h	100	99-100	95-99	85-93	65-70	32	7
500mg q6h	100	100	100	100	72	--	--

Li C, et al. *J Clin Pharmacol.* 2006;46:10:1171-8.

Lodise TP, et al. *Pharmacotherapy.* 2006;26:9:1320-32.

- Probability of target attainment is similar for doses of 1g IV q8h and 500mg IV q6h (both at the desired probability of  $\geq 90\%$ ), up to an MIC of 2 mg/L.
- **Conclusion:** A regimen of 500mg IV q6h is able to achieve a similar probability of target attainment with a decrease in overall drug administered.

# Meropenem Dosing Substitution

- For all adults and children > **50kg** (normal renal function\*):

Medication Ordered	Interchange With
Meropenem 1g q8h	Meropenem 500mg q6h**
Meropenem 1g q12h	Meropenem 500mg q8h**
Meropenem 500mg q8h	Meropenem 500mg q8h**
Meropenem 2g q8h**	Meropenem 2g q8h**
Imipenem 500mg q6h	Meropenem 500mg q6h**
Imipenem 500mg q8h	Meropenem 500mg q8h**
Imipenem 1g q8h	Meropenem 500mg q6h**
Imipenem 750mg q12h	Meropenem 500mg q8h**
Imipenem 250mg q6h	Meropenem 500mg q8h**

- See full protocol details online for pediatric and renal dosage adjustment recommendations.
- If there is any question about the indication for meropenem, the prescriber should be contacted for clarification.



# \*\*Special populations\*\*



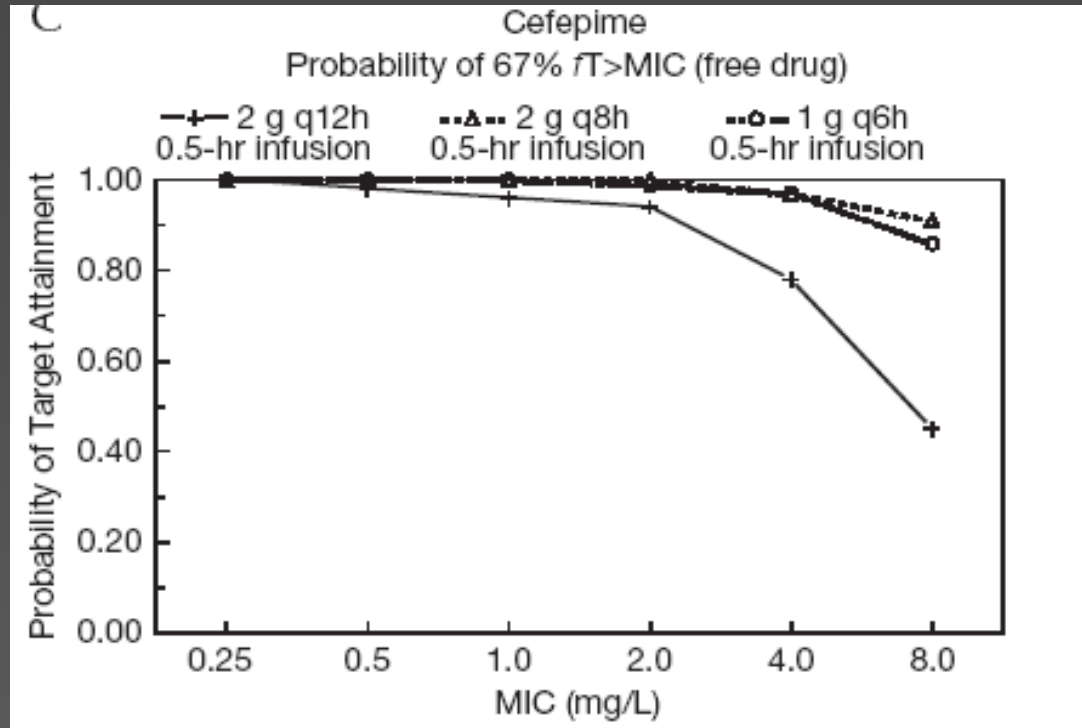
- Meropenem dosing: 2g IV q8hr
- The only indications for which this dose is appropriate are:
  - Meningitis
  - Cystic Fibrosis
  - Micro-organisms with a meropenem/ imipenem MIC of 4mg/L

# \*\*Special populations\*\*

- Examples:

- Prescriber orders meropenem 1g q8hr in a patient w/ meningitis. Dose should be automatically adjusted by the pharmacist to 2g q8hr.
- Prescriber orders meropenem 2g q8hr in a patient w/ sepsis of unknown source. Dose should be automatically adjusted by the pharmacist to 500mg q6hr.
- Prescriber orders meropenem 500mg q6hr for empiric treatment of nosocomial pneumonia. Previous sputum culture yielded *Acinetobacter* with a meropenem MIC of 4 mg/L. Dose should be automatically adjusted by the pharmacist to 2g q8hr and modified to 500mg q6hr if the new culture yields an organism with a lower MIC.

# Cefepime Target Attainment vs. *P. aeruginosa*



Lodise TP, et al.  
*Pharmacotherapy*.  
2006; 26: 1320-32.

- The probability of target attainment is similar for doses of 2g IV q8h and 1g IV q6h, both at a desired probability of  $\geq 90\%$ , up to the susceptibility breakpoint of 8 mg/L and both regimens are superior to 2g IV q12h
- **Conclusion:** A regimen of 1g IV q6h is able to achieve a similar probability of target attainment with a decrease in overall drug administered.

# Cefepime Dosing Substitution

- For all adults and children weighing **> 40 kg** (normal renal function\*):

Medication Ordered	Interchange With
Cefepime 1g q12h	Cefepime 1g q12h
Cefepime 2g q12h	Cefepime 1g q6h
Cefepime 2g q8h	Cefepime 1g q6h
Cefepime 2g q8h for “Neutropenic fever”	Cefepime 2g q8h

\*See full protocol details online for renal dosage adjustment recommendations.

# Cefepime Exceptions

- 1g q12h
  - Dose only appropriate for community-acquired pneumonia not due to *P. aeruginosa* or mild to moderate urinary tract infection. If 1g q12h is ordered for any other indication, dose will be interchanged to 1g q6h.
- 2g q8h
  - Cefepime 2g q 8h allowed **only in “neutropenic fever”**
  - Ordering clinicians **must write** the indication (“neutropenic fever”) after ordering this dose.
  - In patients whom 2 g q 8h is ordered with no indication, pharmacists will review laboratory data as follows:
    - If the Absolute Neutrophil Count (ANC) is  $\leq 500$ , the 2g q8hr dose will be provided. All other orders will be interchanged to 1g q6hr.





# How can we optimize %fT>MIC?

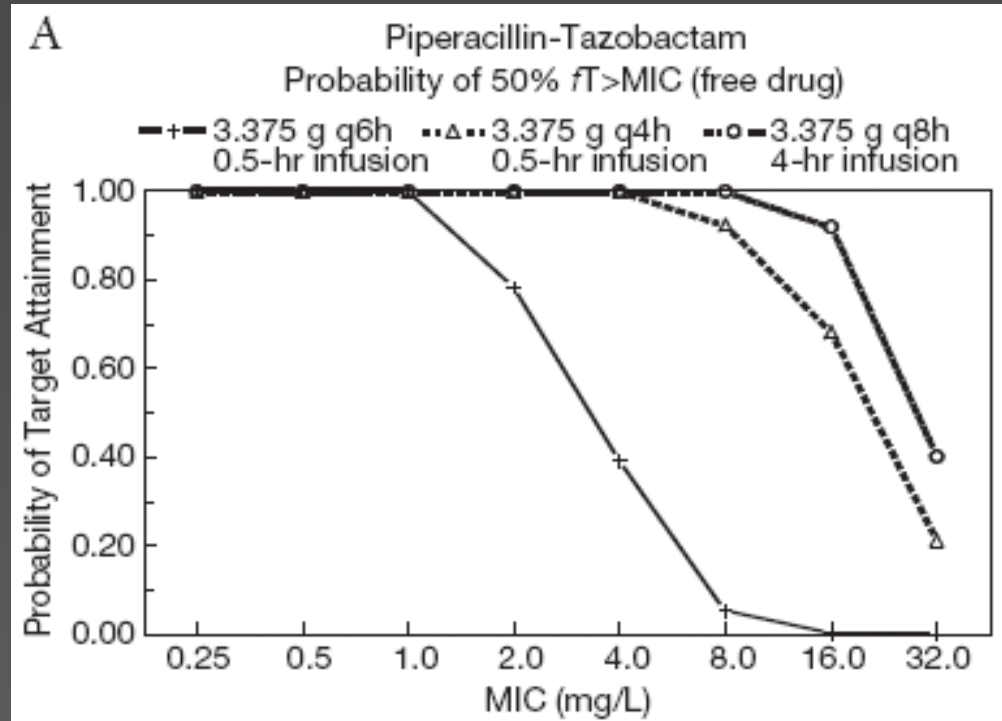


1. Give the drug more frequently (decrease the dosing interval)
2. Extend the infusion of the drug

# Extend the Infusion of the Drug

- Piperacillin/tazobactam
  - Standard dose: 3.375g IV q6h or 4.5g IV q6h over 30min
  - Dosage substitution: 4.5g IV infused over 4h

# Piperacillin/tazobactam Target Attainment vs. *P. aeruginosa*



Lodise TP, *Clin Infect Dis* 2007; 44: 357-363.

- The dose of 3.375g q8h over 4h achieves over 90% probability of target attainment up to an MIC of 16 mg/L versus an MIC of 1 mg/L for the standard dose of 3.375g q6h over 30min.

# Extended infusion:

## Alaris pump considerations

- Problem:
  - When infusing piperacillin/tazobactam over four hours via the Alaris pump, ~20 ml of residual piperacillin/tazobactam remains in the IV infusion set at the end of infusion
    - This represents a significant potential for underdosing

# Extended infusion:

## Alaris pump considerations

- Solution:
  - Administer 4.5g piperacillin/tazobactam in a 100 ml bag
  - This ensures that the patient will still receive the minimum studied dose of 3.375g
    - e.g. If the line is not flushed (~20% of the 4.5g dose is not administered to patient) the patient will still be receiving at least 3.375g

# Piperacillin/tazobactam

## Dosing Substitution

- **All doses** of piperacillin/tazobactam will be interchanged to the following doses for adults and pediatrics > 40kg\*:

Creatinine Clearance $\geq$ 20 ml/min	Creatinine Clearance < 20 ml/min (including HD or PD)	CRRT/SLED
4.5g IV over 4h q8h	4.5g IV over 4h q12h	4.5g IV over 4h q8h

- \* For pediatric patients  $\leq$  40kg, **the normal dose will be given** but will be infused over 4h. NICU patients are excluded from this protocol.

# Piperacillin/tazobactam

## Dosing Substitution

**Exceptions** to extended interval substitution:

1. NICU patients

2. First dose as Surgical Prophylaxis

- PTZ as pre-operative and intraoperative surgical prophylaxis will receive 4.5g over 30 minutes guided by suggested intra-operative dosing intervals
- Post-operative doses will be given using the extended infusion protocol and started 6 hours after the most recent dose

3. First dose in the Emergency Department and Lied Infusion Center

- 4.5g over 30 minutes
- Subsequent doses will be given using the extended infusion protocol and started 6 hours after the initial dose

# Renal Dosage Adjustment

- As delineated in the renal dosage adjustment policy for the respective antibiotics
- Adjustment should be as follows:
  - a. Dosage substitution first
  - b. Renal adjustment next
  - **For example**, meropenem 1g IV q8hr is ordered for a septic patient with CrCl of 30ml/min
    1. Adjust meropenem 1g IV q8hr to 500mg IV q6hr
    2. Then adjust 500mg IV q6h for renal function = 500mg IV q8hr





# In Summary



- In order to optimize the pharmacodynamics of meropenem, cefepime, and piperacillin/tazobactam, dosing substitution protocols have been approved for inpatients at The Nebraska Medical Center.
- The alternate doses provide a high probability of pharmacodynamic target attainment at increased MICs, higher likelihood of positive patient outcomes, and likely contribute to the prevention of antimicrobial resistance while reducing costs.
- Pharmacists are responsible for changing the doses according to the protocols, so please ensure that you are familiar with the protocols.

# For more information...

Visit the Antimicrobial Stewardship Program website for complete dosing protocols:  
[www.nebraskamed.com/asp](http://www.nebraskamed.com/asp)



A screenshot of a web browser displaying the Antimicrobial Stewardship Program website. The browser's address bar shows the URL 'http://www.nebraskamed.com/careers/education/asp/'. The page header features the logo for 'THE NEBRASKA MEDICAL CENTER' and navigation links for 'Manage Your Health', 'Patient Information', 'Health Services', and 'How'. Below the header, a breadcrumb trail reads 'Home &gt; Careers &gt; Education Programs &gt; Antimicrobial Stewardship Program'. The main content area is split into two columns. The left column contains a search bar with a 'GO' button, social media sharing options (SHARE, Facebook, Twitter, Email), and a vertical menu of links: 'Antimicrobial Stewardship Program', 'Antibiograms (Restricted)', 'Antimicrobial Restrictions', 'Antimicrobial Guidebook', 'Clinical Pathways', 'Dosing Protocols', 'Other Information', 'ASP News', 'Meet Our Team', and 'ASP Abstracts &amp; Publications'. A yellow arrow points to the 'Dosing Protocols' link. The right column features a large graphic with the text 'striking back at antimicrobial resistance' and a petri dish containing blue and yellow agar. Below this, the heading 'Antimicrobial Stewardship' is partially visible, followed by the sub-heading 'Antimicrobial Resistance' and a quote: '"Antimicrobial resistance costs money, livelihood, and undermines the effectiveness of health delivery programs described as a threat to global stability and national security. Antimicrobial use is the key driver of resistance. This selective pressure is a combination of overuse... and also from misuse."' The quote is attributed to the 'WHO Global Strategy for Containment of Antimicrobial Resistance'.

# For more information...

- Visit the Pharmaceutical & Nutrition Website
  - View the dosage substitution policies

The screenshot shows a web browser window displaying the website for the Nebraska Medical Center's Pharmaceutical & Nutrition Care department. The browser's address bar shows the URL <http://www.preceptor.com/other/pharmadm/rxhome/index.html>. The website header includes the Nebraska Medical Center logo and the text "Pharmaceutical & Nutrition Care". A navigation bar below the header contains links: "The Nebraska Medical Center", "Intranet Home", "Synapse", "UNMC", and "UNMC Intranet". The main content area is divided into two sections. On the left is a table of links, and on the right is a grid of ten blue circular buttons. A yellow arrow points from a mortar and pestle icon labeled "Rx" to the "Therapeutic Interchange & Dosage Substitution" button.

About Pharmacy	
<a href="#">Addition to Formulary Request Form</a>	
<a href="#">Medication Screening for Diagnostic/Procedure areas</a>	
<a href="#">Tylenol Content of combination pain products</a>	
<a href="#">Banned Abbreviations</a>	
<a href="#">Electronic Refrigerator Thermometer Info.</a>	
<a href="#">Error Reporting</a>	
• <a href="#">antineoplastic extravasation</a>	
• <a href="#">non-antineoplastic extravasation</a>	
<a href="#">Formulary Services</a>	
<a href="#">IV Cards</a>	
<a href="#">IV-PO Pocket Card</a>	
<a href="#">Look and Sound Alike Medications</a>	
<a href="#">Micromedex</a>	
<a href="#">Clinical Pharmacology</a>	
<a href="#">P&amp;T Approved Guidelines/Protocols</a>	

<a href="#">Antimicrobial Stewardship Program</a>	<a href="#">Clinical Pharmacy</a>	<a href="#">Drug Information Service</a>	<a href="#">Therapeutic Interchange &amp; Dosage Substitution</a>	<a href="#">Medical Staff Approved Formularies</a>
<a href="#">Clinical Nutrition</a>	<a href="#">Departmental Policies &amp; Procedures</a>	<a href="#">Publications &amp; E-Mail Archives</a>	<a href="#">Departmental Applications Main Menu</a>	<a href="#">Departmental Applications Web Access</a>



# If you have any questions...



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