Antimicrobial therapy

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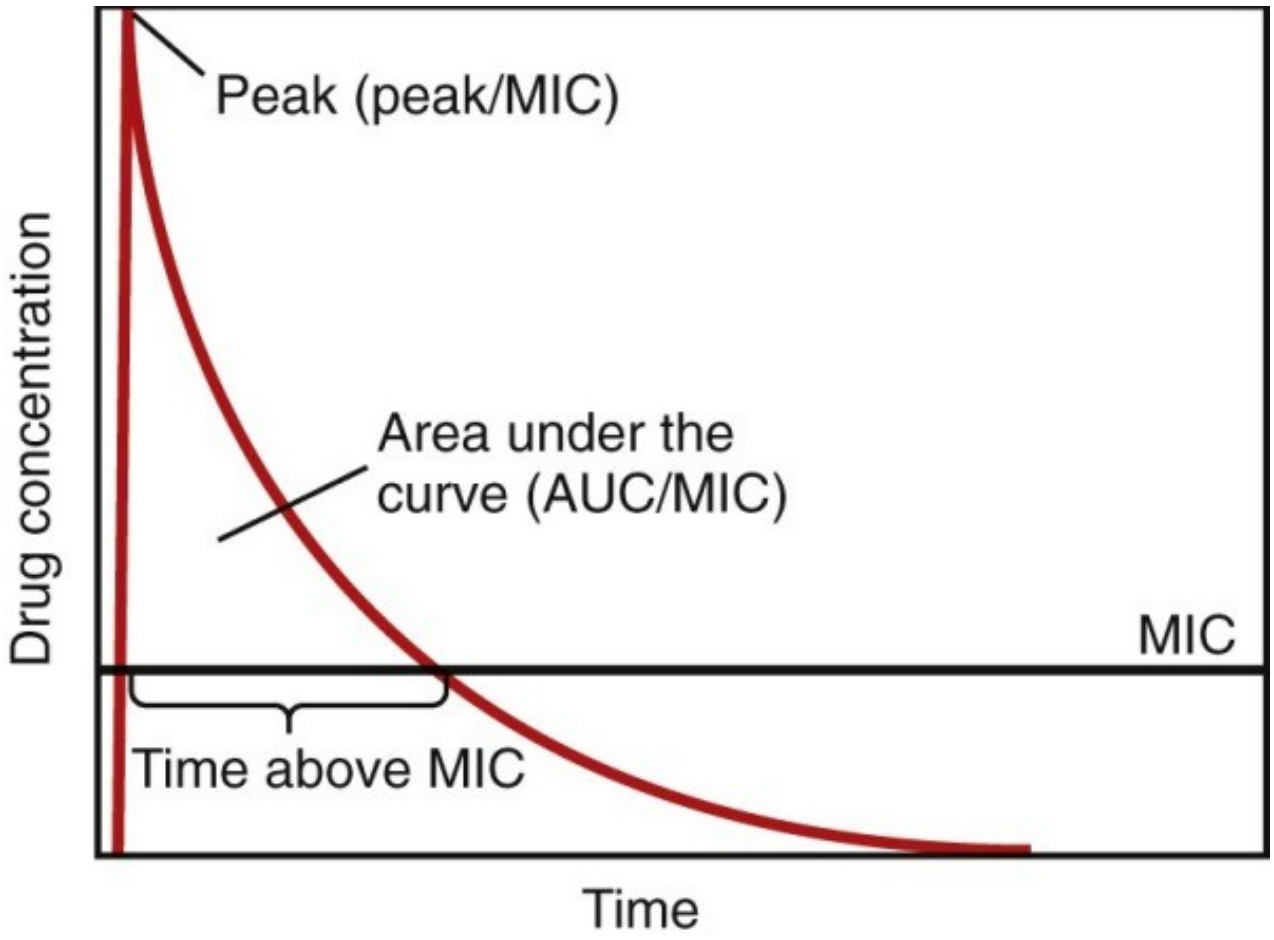
Objectives

- Introduction to basic antimicrobial principals
  - Pharmacokinetics (PK)
  - Pharmacodynamics (PD)
- Provide an overview of some the most common antimicrobial drug classes
  - ß-lactam AB
  - AG
  - FQ
  - A few others

Background

- Basic mechanism of action
  - Time-dependent killing
  - Concentration-dependent killing
- PK
  - Peak & Through serum concentrations
  - Half-life (T1/2)
  - Source of metabolism
  - Source of excretion (kidney, GI, etc)
- PD – relationship between PK & minimum inhibitory concentration (MIC)

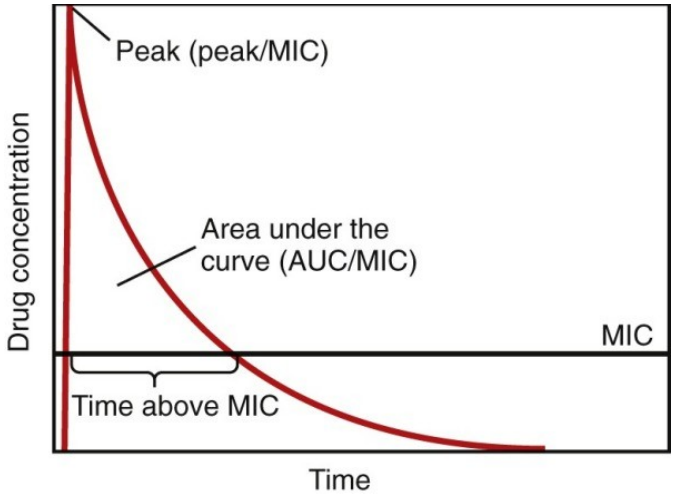
PD principals



1. Area under the curve (AUC/MIC)
2. Time above MIC
3. Peak MIC

PD goals

Parameter	***Goal***	***AB Drug Classes***
Time above MIC	> 50-60% of the dosing interval	• All ß-lactams • Macrolides • Linezolid
Peak conc. : MIC ratio	≥ 10:1	• AGs vs G- organisms
Area under the Curve (AUC) : MIC ratio	• ≥ 30-50:1 • ≥ 125:1	• FQ vs G+ orgs • FQ vs G- orgs.



FD

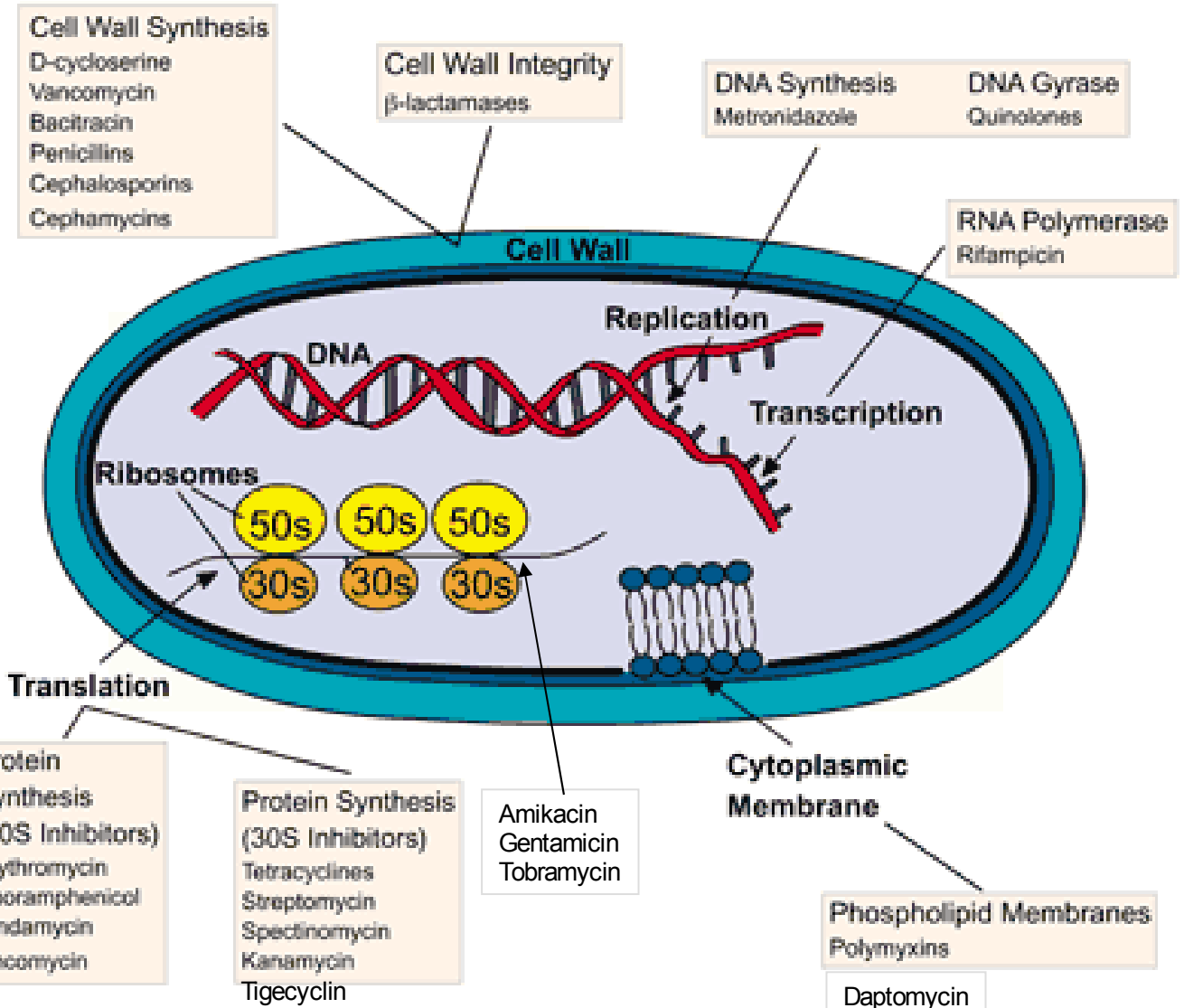
- Conc. dependent killing agents
  - FQ, AG, ML, metro, dapto
  - Eliminate bacteria when their conc.-s are well above the MIC of the organisms

- Time dependent killing agents
  - P, CS, aztreonam, vanco, carbapenems, ML, linezolid, tige, doxy, clinda
  - Kill G- bacteria only when the conc. at the site of the bacteria is higher than the MIC of the organisms

Mechanisms of action

Mechanism of action	***Antibacterial Family***
Inhibition of cell wall synthesis	-ß-lactams -Vancomycin
Inhibition of protein synthesis	-AG -Linezolid -Tetracyclin
Inhibition of DNA synthesis	-FQ
Inhibition of folic acid synthesis	-TMP/SMX
Inhibition of RNA synthesis	-Rifampicin
Disruption of cell membrane integrity	-Daptomycin -Polymyxin B, E (Colistin)
Others	-Metronidazole -Nitrafurantoin

Mechanisms of action



Antibiotic therapy

- Identify causative agent
- Evaluate drug sensitivity
- Target site of infection
- Drug safety/side effect profile
- Patients factor
- Cost

Factors in Selecting Initial Appropriate Therapy

- Patient features: Choose empirical therapy that is based on site and severity of infection and clinician assessment of the likelihood for deterioration and mortality.
- Local susceptibility and epidemiology: Choose empirical therapy to cover the likely infecting pathogen based on local susceptibility patterns while considering prior antibiotic therapy.
- Initial antibiotic therapy dosing and duration: Choose initial empirical therapy that will deliver enough antibiotic to the site of infection and

  be well tolerated (consider AB penetration)
- Combination vs. monotherapy: Initial AB choose should give broad enough coverage, avoid emergence of resistance, and have the potential for synergy if necessary (TB, IE, Sepsis, Anthrax …)

General principles when considering How to de-escalalate

- Identify the organism and know its susceptibilities; recognize any limitation in the available microbiology support system (eg, length of time to receiving antibiogram)
- Assess and potentially modify initial selection of ABs based on organism susceptibility report
- Make the decision in the context of patient progress on the initial regimen
- Individualize the duration of therapy based on patient factors and clinical response

Guideline-Based De-escalation

- Before guideline: 50 patients, standard treatment
- After guideline: 52 patients, treatment guideline
- Culture
- Empirical therapy
  - Vanco + IMP + CIP
  - 90% coverage based on local resistance data
- Therapy reassessed after 24-48 hours
  - De-escalation recommended and usually occurred
- 7-day duration recommended
  - Unless signs and symptomps persist

Ibrahim EH et al. Crit. Care Med 2001,29:1109-1115

Penicillins

- Bactericidal cell-wall synthesis inhibitors
- G+ activity maintened across spectrum
- G- activity dependent on ability to cross porin channels
- ß-lactamase inhibitor combinations:
  - MSSA coverage
  - Enhanced anaerobic activity
- Therapeutic concentration in most tissues
- Poor CSF penetration
- Renal excretion

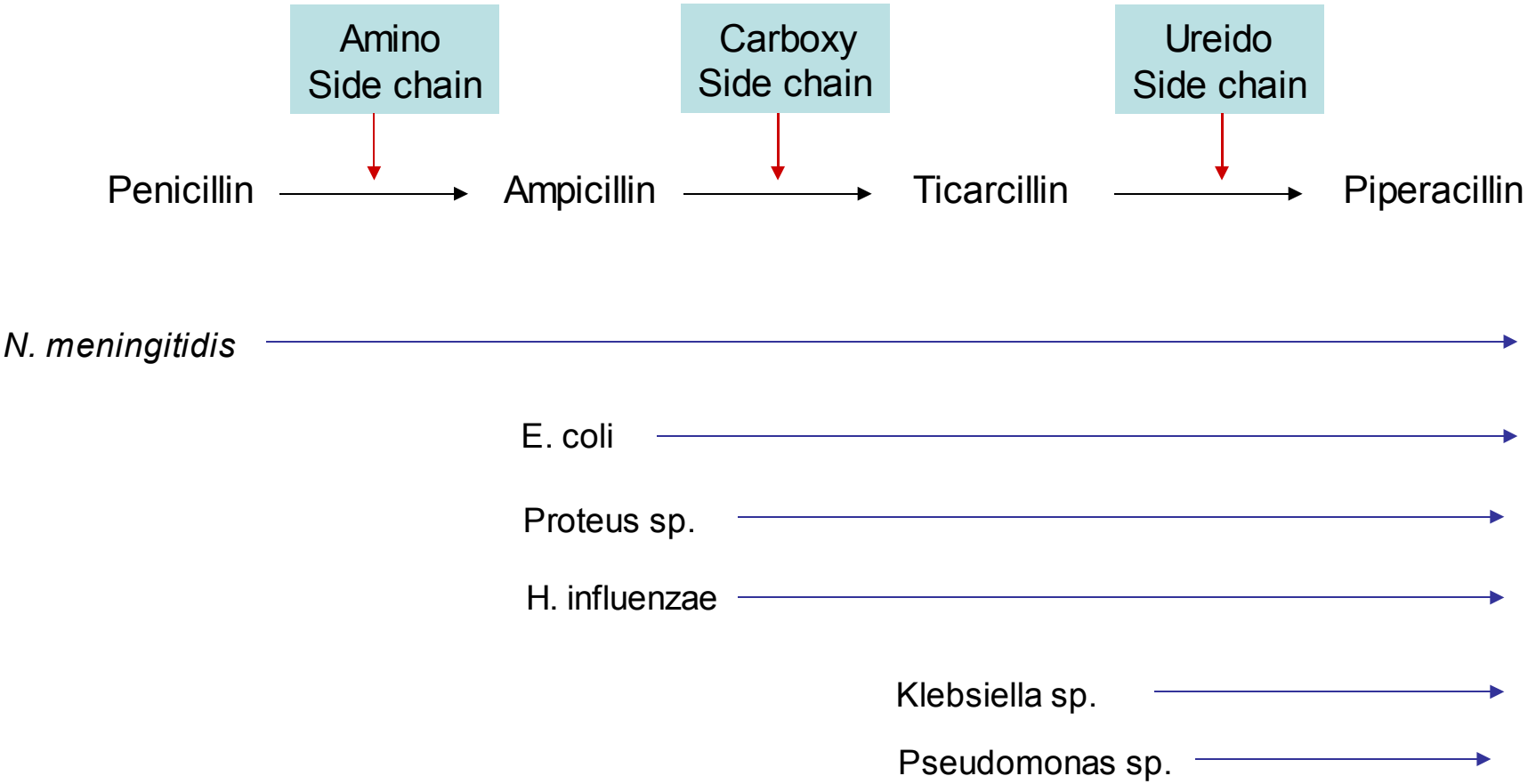
Activity of Penicillins against selected bacilli

	Usual **Minimal Inhibitory Concentration (ug/ml)**				
Organism	**Pen G**	**Pen. V**	**Amp, Amoxi**	**Oxacillin**	**PIP**
S. pneumoniae	0,01	0,02	0,02	0,04	0,02
S. pyogenes	0,005	0,01	0,02	0,04	0,02
S. agalactiae	0,005	0,01	0,02	0,06	0,15
Viridians streptococci	0,01	0,01	0,05	0,1	0,12
MSSA	0,025	0,02	0,05	0,3	0,8
MRSA	> 25	> 25	> 25	0,4	25
N. meningitidis	0,05	0,25	0,05	6,0	0,05

Activity of Penicillins against selected bacilli and anaerobic organisms

	Mean Minimal Inhibitory Concentration (ug/ml)				
Organism	**Pen G**	**Amp, Amoxi**	**Oxacillin**	**Ticarcillin**	**PIP**
Cl. perfringens	0,5	0,05	> 0,5	0,5	0,05
Corynebact. diphteriae	0,1	0,02	> 0,1	0,1	1,0
L. monocytogenes	0,5	0,5	> 4,0	4	0,5
H. influenzae	0,8	0,5	> 25	0,5	0,1
Fusobacterium nucleatum	0,5	0,1	> 100	0,5	0,5
B. fragilis	32	32	> 500	64	32

Pen; G-
Spectrum of activity



Penicillins

- Major adverse Events
  - Anaphylaxis
  - Rash and/or urticaria
  - Seizures
  - Nephritis
  - Platelet dysfunction
- Anti-Staphylococcus aureus Penicillins
  - Resistant to ß-lactamase
  - NO G- acitivity

  - Nafcillin (4x2 g/d, IE= 6x2 g/d iv.) – (No renal adjustment)
  - Oxacillin „ „

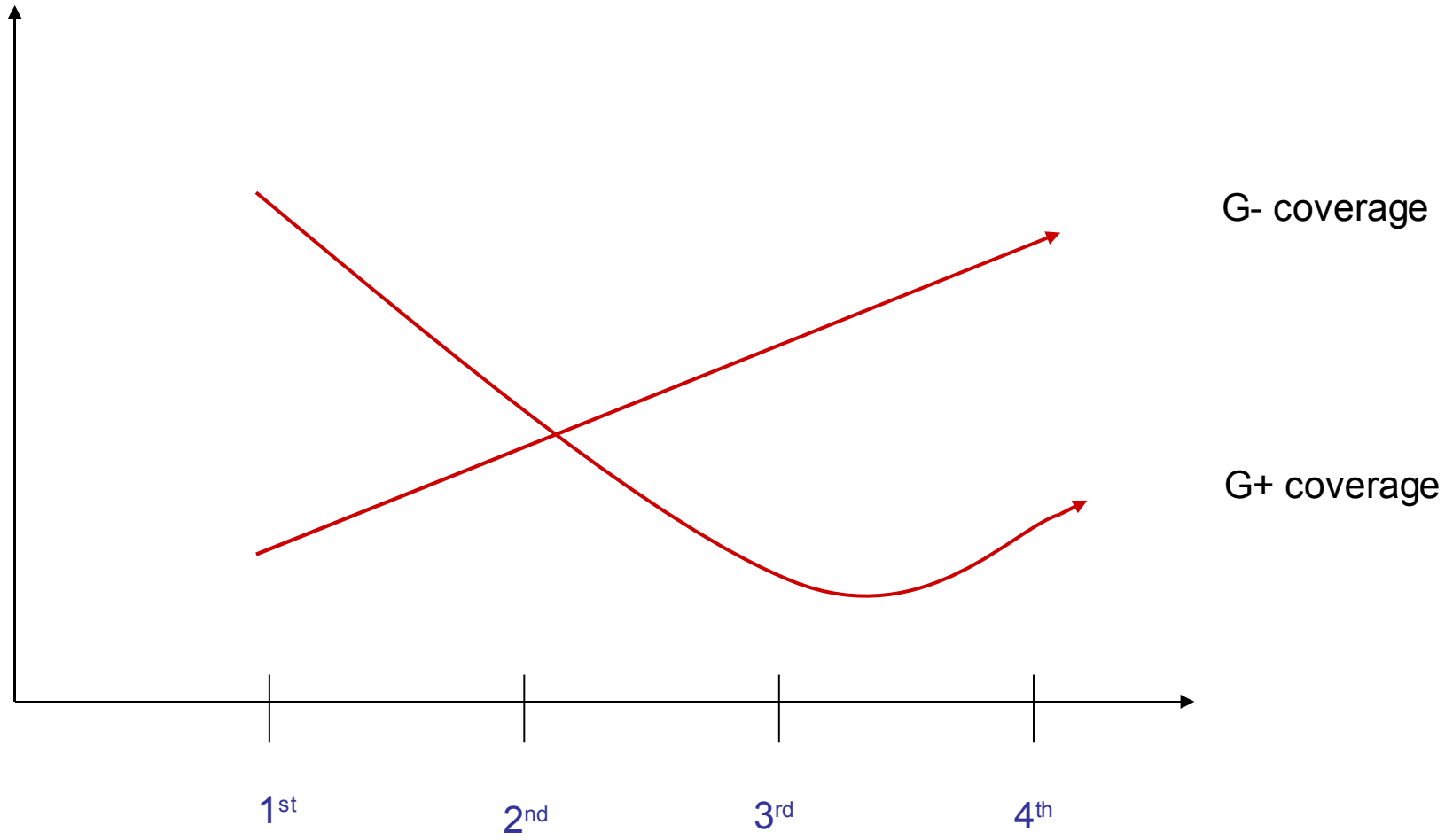
Extended-spectrum Penicilins

- Piperacillin/Tazobactam
  - Sodium content (1.85 mEq/g)
  - Dosing
    - Serious infections (Pneumonia): 4x4,5 g/d
    - Other infections: 4x3,375 g/d
- Ticarcillin/Clavulanic acid
  - Sodium content (5,2 mEq/g)
  - 2nd line agent for *S. maltophilia*

Cephalosporins

- Bactericidal cell-wall synthesis inhibitors
- DO NOT treat *Enterococcus* spp.
- G+ activity generally decreases with each generation
- G- activity increases with generation
- Weak anaerobic activity with 2 generation

Cephalosporin Spectrum of activity



Cephalosporins

- 1st generation (ex: cefazolin)
  - Excellent MSSA activity
  - Some G- activity – E. coli, Klebsiella
  - Major role in surgical systemic prophylaxis

- 2 generation (ex: cefotetan, cefoxitin, cefuroxim)
  - Good G-, moderate G+ and anaerobic coverage
  - Primarily used for abdominal surgery prophylaxis

Cephalosporins

- 3rd generation (ex: ceftriaxon, ceftazidim)
  - 1st ß-lactams with Pseudomonas coverage (ceftazidim)
  - Ceftazidim selects out MDR organisms (MDR organisms (MDR G-, VRE, C. difficile, MRSA)
  - Ceftriaxon
    - Excellent CSF penetration
    - Excellent S. pneumoniae activity
- 4th generation (ex: cefepime)
  - Excellent MSSA and *P. aeruginosa* sp. coverage

Cephalosporins

- Major Adverse Events
  - Rash
  - Anaphylaxia
  - Seizures

- Cross-Sensitivity with Pen-s
  - 1-10%
  - Concern if patient has history of anaphylaxia

Carbapenems

- Bactericidal cell-wall synthesis inhibitors
- Broadest-spectrum antimicrobials available
- Stable against most ß-lactamases
- Some intrinsic Resistance
  - *Enterococcus faecium*
  - *MRSA*
  - *S. maltophilia*
  - *Burkholderia* spp.
  - Penicillinase-resistant *S. pneumoniae*

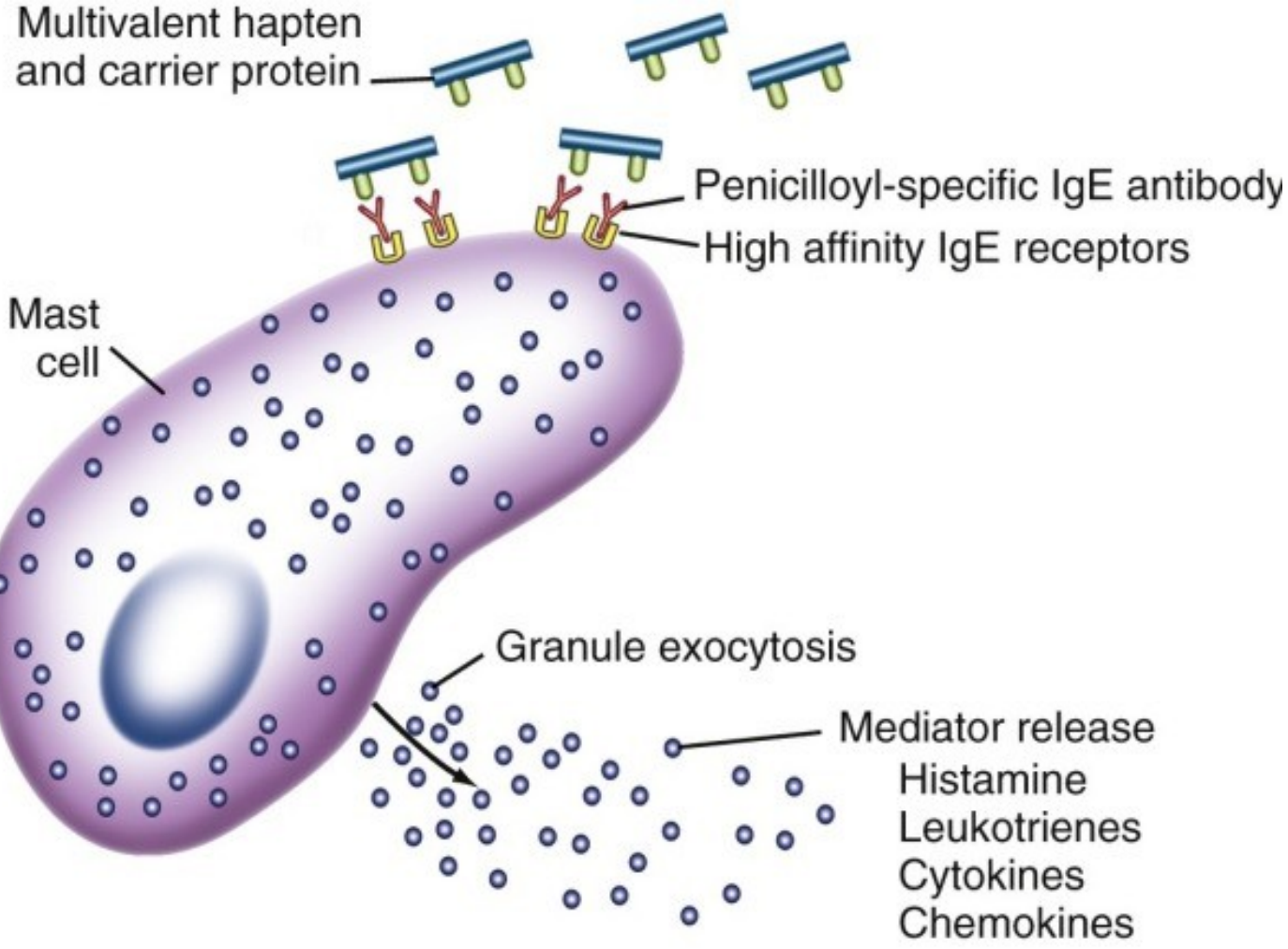
Carbapenems

- 4 drugs
  - Imipenem/Cilastatin
  - Meropenem
  - Ertapenem (NOT use for P. aerugonisa)
  - Doripenem
- Incomplete class cross-resistance
  - Ex: P. aerugonisa

Classification of allergic reactions to ß-lactam ABs based on time of onset

Reaction type	Onset after drug adm. (hr)	Clinical reactions
Immediate	0-1	Anaphylaxis Hypotension Laryngeal edema Wheezing
Accelerated	1-72	Urticaria, angioedema Laryngeal edema Wheezing
Late	> 72	Morbilliform rash Interstitial nephritis Hemolytic anemia Neutropenia Thrombocytopenia Serum sickness Drug fever Stevens-Johnson sy Exfoliative dermatitis

ß-lactam allergy



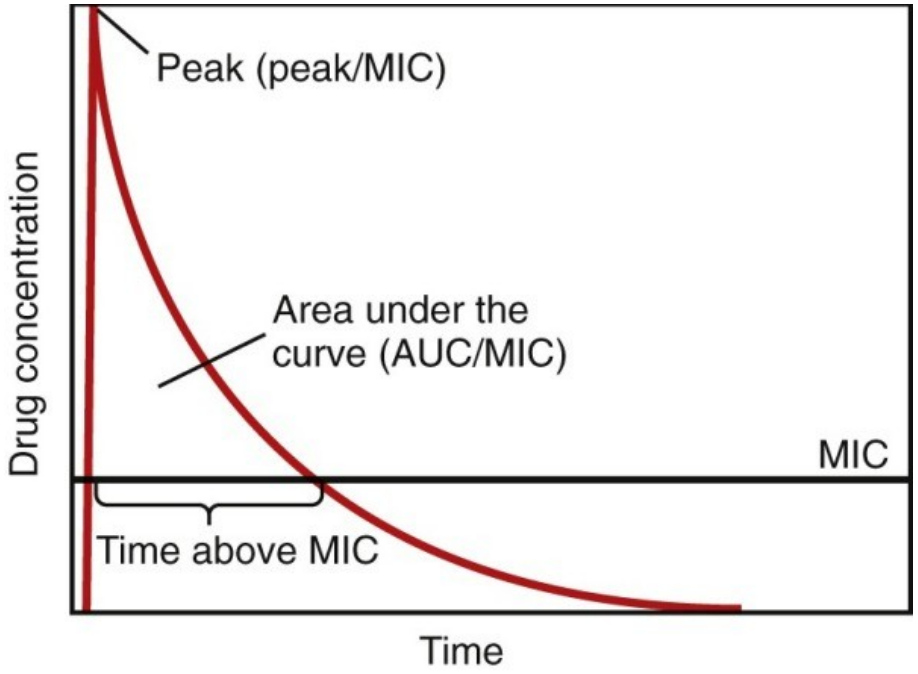
Monobactam

- Aztreonam
- Bactericidal cell-wall synthesis inhibitors
- Pure G- coverage
  - Including Pseudomonas
- No cross-sensitivity with penicillins/CS
- Major AE
  - Rush
  - GI upset
  - Injection-site thrombophlebitis

Fluoroquinolones

- DNA synthesis inhibitors
  - DNA-gyrase inhibitor in G- bacteria
  - Topoisomerase IV inhibitor in G+ bacteria
- Concentration dependent killers
  - G- AUC/MIC Goal ≥ 125:1
  - G+ AU/MIC Goal ≥ 10:1

Fluoroquinolones



Cipro 400 mg iv. – AUC~ 25

Pseudomonas MIC ≤ 0,25
Urine AUC/MIC = 100:1
Sputum AUC/MIC = 10:1
(only ~ 10% penetration)

Anti-Pseudomonal agents

* CIP
* Levofloxacin (<)
* trovafloxacin (!)

Fluoroquinolones

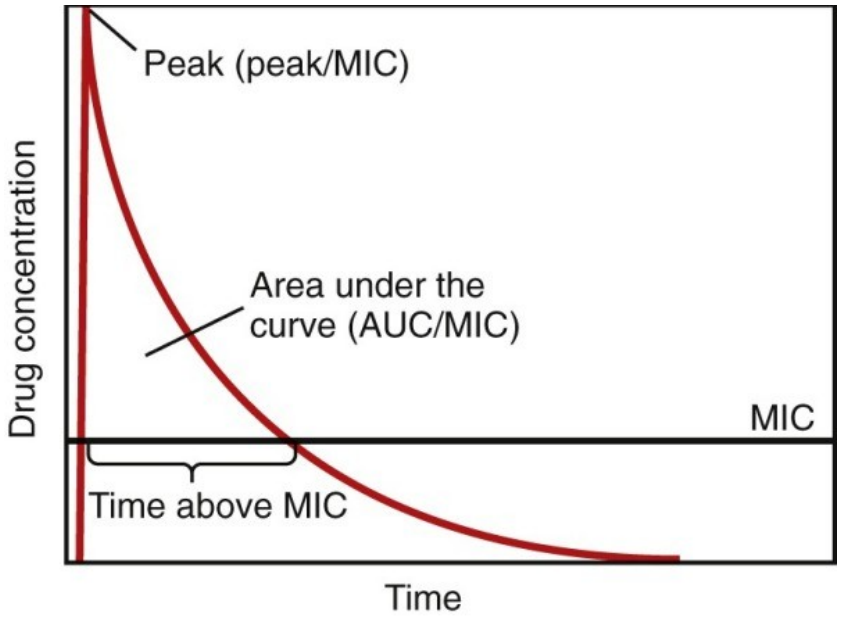
- G+ coverage
  - Class has POOR S. aureus drugs
  - Select out MRSA
  - Newer agents excellent S. pneumoniae coverage

- Major AE:
  - QT prolongation
    - Moxifloxacin >>> levofloxacin >>> ciprofloxacin
  - C. difficile colitis

- Drug interaction
  - phenytoin;
  - warfarin

Aminoglycosides

- Inhibit bacterial protein synthesis at 30S & 50S ribosomal subunits
- Concentration-dependent killers
  - Goal Peak:MIC = 10:1
  - PAE



Aminoglycosides

- Place in Therapy:
  - Treatment of G- infections
  - Gentamicin for G+ synergy in combination with a ß-lactam or vancomycin
- Major AE
  - Nephrotoxicity (high through)
  - Otoxicity (prolonged duration of therapy)
- Drug IA
  - Neuromuscular blockers

Aminoglycosides

- Gentamicin/Tobramycin
  - G- non-Burn 7 mg/kg iv q24 h
  - G- Burn: 2,5-3 mg/kg iv. 8-12 h
  - Gentamicin G+ Synergy: 1 mg/kg iv. q8 h

- Amikacin
  - G- non-Burn: 15-20 mg iv. q24
  - G- Burn: 7.5 mg/kg iv. Q8

- Dose calculator: www.surgicalcriticalcriticalcare.net

Aminoglycosides

- Colistin (Polymyxin E)
  - Reserved for MDR G- organisms
  - Nebulized: 150 mg inhaled q12 h
  - Iv. (VERY nephrotoxic): 2-3x2,5 mg/kg/d
- Polymyxin B
  - Also reserved for MDR G- organisms
  - Iv: 2x15.000 – 25.000 U/kg/d
- No way to monitor levels for iv. polymyxins

Aminoglycosides

- Polymyxin B & Colistin
  - Major AE
    - Nephrotoxicity
    - Neurotoxicity
  - Drug IA
    - Neuromuscular blockers

Vancomycin

- Inhibits bacterial cell wall synthesis
- Time-dependent killer (time above MIC)
  - Some concentration-dependent characteristic
    - P, CS, aztreonam, vanco, carbapenems, ML, linezolid, tige, doxy, clinda
    - Kill G- bacteria only when the conc. at the site of the bacteria is higher than the MIC of the organisms
  - Uses
    - Iv: treatment of G+ infections
    - Per os: treatment of C. difficile colitis

Vancomycin

- Dosing
  - Iv: 20 mg/kg iv 1x, than 15 mg/kg, iv – q8-12 h
  - Per os: 4x125-250 mg/die

- Major AEs
  - Red Man syndrome – slow down infusion
  - Not neprotoxic – but accumulates

Vancomycin dosing

The Mayo Medical Center vancomycin dosing nomogram*	
Creatinin clearence ** (ml/min)	Dosing interval
> 80 65-80 50-64 35-49 21-34	Every 12 h Every 12 to 18 h Every 24 h Every 24-36 h § Every 48 h §
* Use of 15 mg/kg; The dosing interval is based on renal function	
**The estimated renal function is near the border of two dosing intervals Cr Cl: (140 – age) x lean body weight (x 0,85 for females) / se creatinin	
§ Patient with serious infection, whom the initial dosing interval is >24 h should have serum level monitoring	

Mayo Clinic 1999

Linezolid

- Oxazolidinone – inhibits bacterial protein synthesis
  - Bacteriostatic: *Enterococcus* sp., *Staphylococcus* sp.
  - Bactericidal: *Streptococcus* sp.

- Large volume of distribution
- Dosing: 2x600 mg Iv/Per os

Linezolid

- Major AE
  - Thrombocytopenia/pancytopenia
  - Blurred vision
  - Serotonin Syndrome

- Drug IA
  - Selective Serotonin Reuptake Inhibitors (SSRIs)

Quinupristin/Dalfopristin (Synercid®)

- Inhibits bacterial protein synthesis
- Major organisms:
  - VRE
  - MSSA & MRSA
  - S. pyogenes
- Dose
  - 7,5 mg/kg iv q8-12 h (no renal adjustment)
- Major AE
  - Hyperbilirubinaemia
  - Infusion site reaction
  - Infusion-related arthralgias/myalgias
- Drug IA
  - No significant

Daptomycin

- Cell membrane disruption leading to inhibition of DNA/RNA/protein synthesis - Lipopeptide
- Spectrum of activity
  - MRSA
  - VRE
- Indications
  - Bacteremia
  - Endocarditis
  - Skin/Soft tissue infection
- Does NOT treat pneumonia!

Daptomycin

- Dose
  - 4-6 mg/kg iv q24 h
  - Adjust for renal dysfunction
- Major AE
  - Anemia
  - Constipation/Nausea/Vomiting
  - Elevation of CPK, myalgia
  - Injection-site reaction

Sulfamethoxazole/Trimethoprim

- Interferes with bacterial folic acid synthesis (Bactrim®)
- Drug of choice
  - S. maltophilia
  - PCP
- Alternative: for MRSA

Sulfamethoxazole/Trimethoprim

- Dosing
  - Based on TMP component
  - UTI: 800/160 (DS) 2x1 tbl.
  - Severe infections
    - MRSA/PCP/S. maltophilia
      - 5 mg TMP/kg iv/po q6-8 h
  - Adjust for renal dysfunction

- Major AE
  - Stevens-Johnson sy.
  - Rash
  - Hyponatremia
  - Hyperkalemia
  - GI upset (large PO dose)

Tetracycline

- Inhibit bacterial protein synthesis
- Bacteriostatic
- Spectrum of activity
  - G+ including MRSA
  - G- (including Borrelia sp.)
  - Atypicals (*Mycoplasma, Chlamydia, Rickettsia*)
  - Alternative for *H. pylori*

Tetracycline

- 3 agents
  - Tetracycline 250-500 mg po q6 h
  - Doxycycline 100 mg po/IV q12 h
  - Minocycline

- Major AE
  - Photosensitivity
  - Teeth/enemal discoloration in children (< 12 y)
  - Hepatotoxycity

Tigecycline

- Glycylcycline – structurally similar to tetracyclines
- Protein synthesis inhibitor
- Bacteriostatic
- Spectrum of activity
  - G+, including MRSA, VRE
  - G-, including MDR A. baumannii, E. coli, Klebsiella
  - Anaerobes
- Does not cover
  - Pseudomonas sp.
  - Proteus sp.

Tigecycline

- Indications
  - Complicated skin and soft tissue infections
  - Complicated intraabdominal infections
  - CAP (FDA in march 2009 approved)

- Dose
  - 100 mg iv x1, than 50 mg q12 h

- Major AE
  - N/V
  - Abdominal pain
  - Super infections (*P. aeruginosa, Proteus*)

Macrolides

- Inhibit RNA-dependant protein synthesis
- Spectrum of activity
  - G+; including MSSA
  - G- (H. influenzae)
  - Atypicals (Legionella, Mycoplasma, Chlamydia sp.)

- Several Agents
  - Erythromycin
  - Clarithromycin
  - Azithromycin

Macrolides

- Erythromycin
  - Used for Adverse Drug Event – GI motility
  - Used for surgical prophylaxis with neomycin (in Hungary – not)
- Azithromycin
  - CAP
  - Bronchitis, sinusitis
- Clarithromycin
  - CAP
  - Bronchitis, sinusitis
  - H. pylori eradication
- Major AE
  - Abdominal pain/cramping (E >> C >> A)
  - N/V/Diarrhea
  - Headache

Clindamycin

- Inhibits bacterial protein synthesis
- Spectrum of activity
  - G+; MSSA, Sterptococcus sp., some MRSA
  - Anaerobes
- Excellent alternative for Penicillin allergic patients
- Major AE
  - Diarrhea (C. diff.)

Metronidazole

- Interacts with DNA causing strand breakage and ultimately inhibits protein synthesis
- Spectrum of activity
  - C. difficile diarrhea
- Major AE
  - N/V
  - Diarrhea
- Dosing
  - C. difficile: 500 mg po q6 h

Antimicrobal Resistance

- Unsuppressed production of ß-lactamase
  - AMP-c
  - ESBL
- Alteration in bacterial cell membrane
  - Vancomycin-resistant Enterococcus
- Pseudomonas sp.
  - AG-altering enzymes
  - Efflux-pump – pump out drug
  - Alter porin channel – drug can’t get it

Antibiotic prophylaxis

- Post-op wound infection is the second most common nosocomial infection
- Cost of this complication >
- Prolongs hospital LOS by ~ 15 days
- Cover bacterial flora involved in the surgical field
- Administer within 1 hours before
- Maintain therapeutic blood level during lengthy procedures
- Continue prophylaxis for the 24 hour period surrounding surgery

Take Home Points 1.

- Penicillins – R increase G- and maintain G+
- Addition of ßL inhibitor = anaerobic coverage
- CSs – avoid 3rd generation overuse
- Carbapenems – reserve for last resort (NB: sepsis: often empiric therapy)
- Vancomycin – aim high trough conc.
- PD-based drug dosing

Take Home Points 2.

- Antibiotic resistance often leads to worse patient outcomes
- Based on well-described epidemiology, control measures include:

: Hand hygiene

: Isolation precautions

: Prudent antimicrobial use

: Prevention of device-related (eg. vascular, catheter) infections

: Environmental clearing