Antimicrobial treatment in 2011

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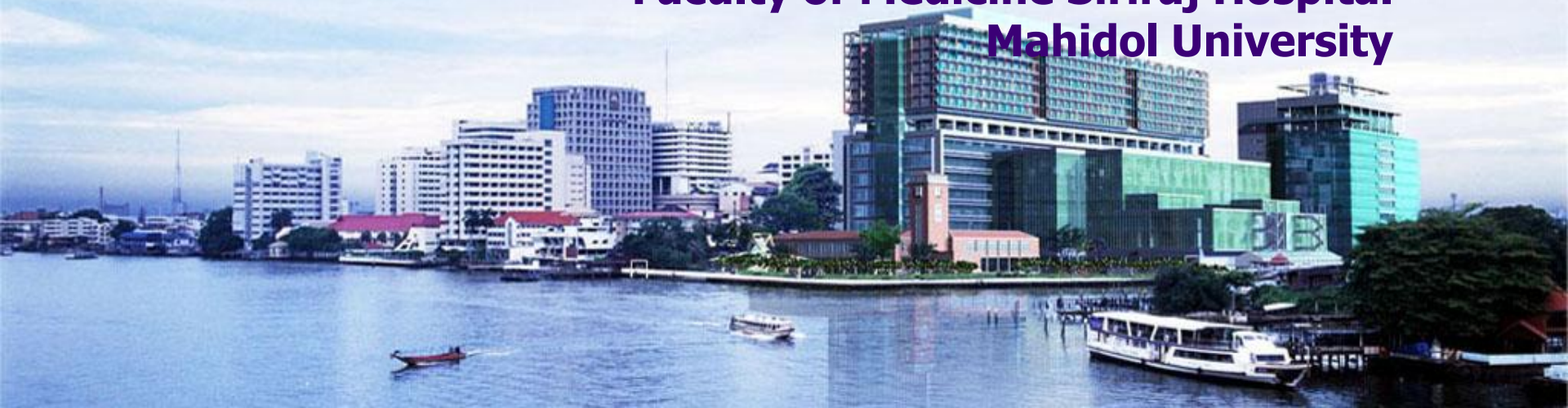


Optimal Antibiotics Administration

- Patient (Host) factors
- Basic principles of Pharmacokinetics & Pharmacodynamics
- Types of Antibiotics
- Drug selection
- Appropriate use; timing and duration
- Organism factors: drug-resistant

Optimal Antibiotics Administration

- **Patient (Host) factors**

Optimal Antibiotics Administration

- **Patient (Host) factors**
  - advanced age
  - chronic and/or severe disease
  - polypharmacy
  - immunodeficiency
  - received prior surgical or medical interventions (i.e., blood products, oncologic, or rheumatologic medications)

Optimal Antibiotics Administration

- **Patient (Host) factors**
  - The prior use of antibiotic therapy **->** increased risk of antibiotic-resistant pathogen infection
  - More severe of the illness

    - extended hospital stay
    - frequently of intubation
    - parenteral nutrition, or other medical devices (i.e., central venous or urinary catheters)

  - Increase the risk of a hospital acquired infection (HAI) with a drug-resistant pathogen

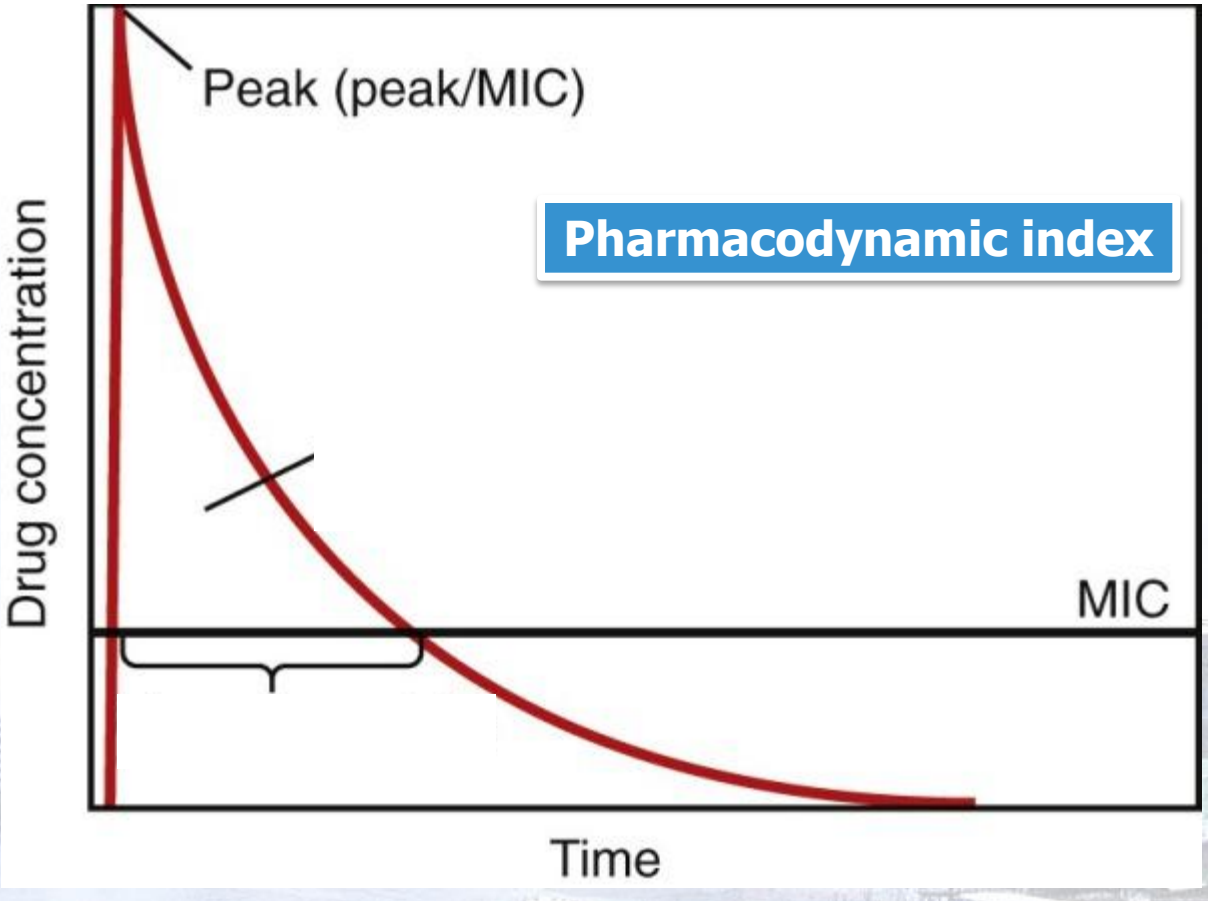
Optimal Antibiotics Administration

- Basic principles of Pharmacokinetics & Pharmacodynamics
- Types of Antibiotics

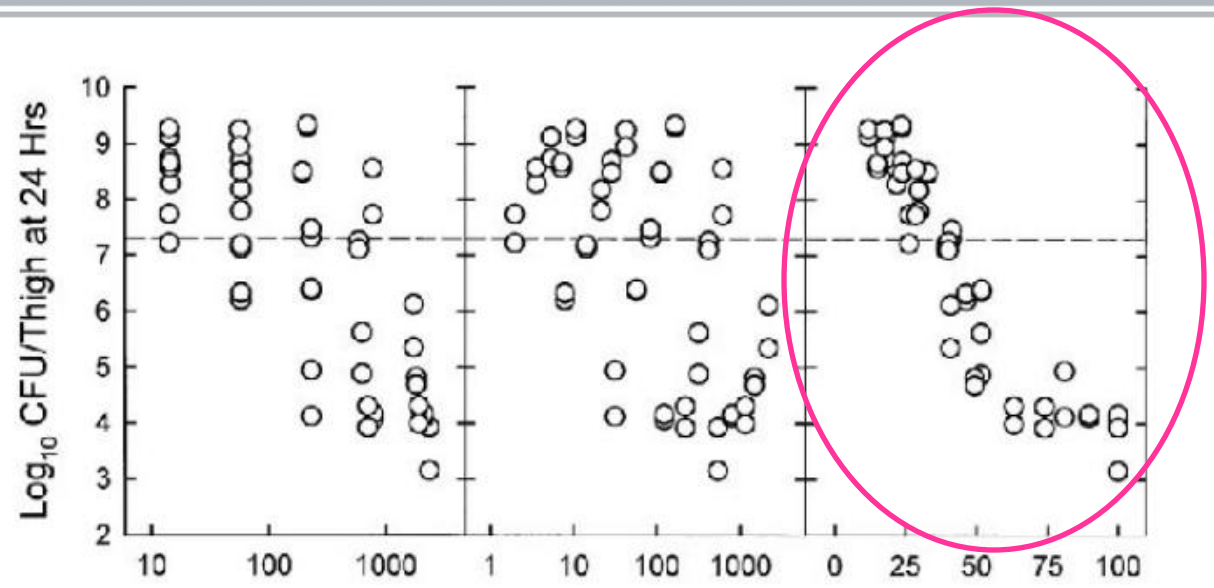
- Drug selection

Basic principles of Pharmacokinetics & Pharmacodynamics

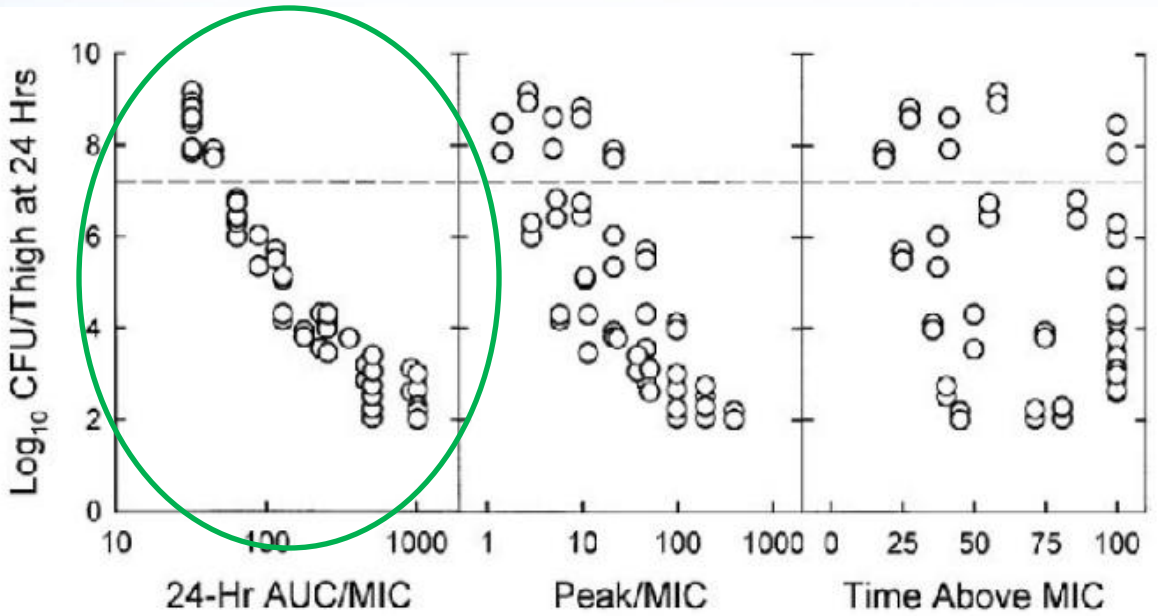
Common antibiotic pharmacokinetic and minimal inhibitory concentration (MIC) pharmacodynamic relationships



Basic principles of Pharmacokinetics & Pharmacodynamics



Ceftazidime
vs
K. pneumoniae

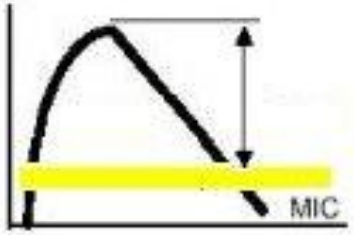


Levofloxacin
vs
S. pneumoniae

Basic principles of Pharmacokinetics & Pharmacodynamics

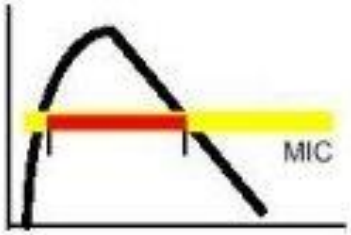
Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

Peak/MIC



- Aminoglycosides

T > MIC



- Beta-lactams
- Clindamycin
- Erythromycin
- Linezolid

24h-AUC/MIC

- Azithromycin
- Quinolones
- Vancomycin

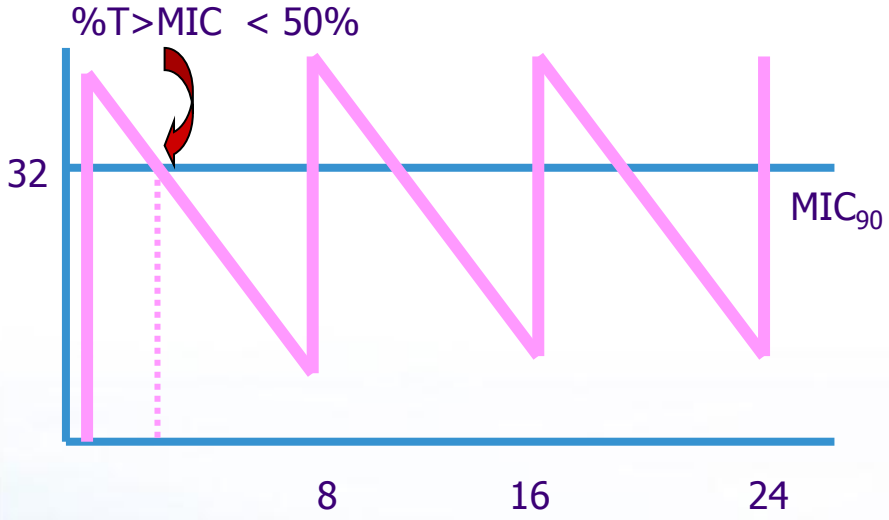
Optimal Antibiotics Administration

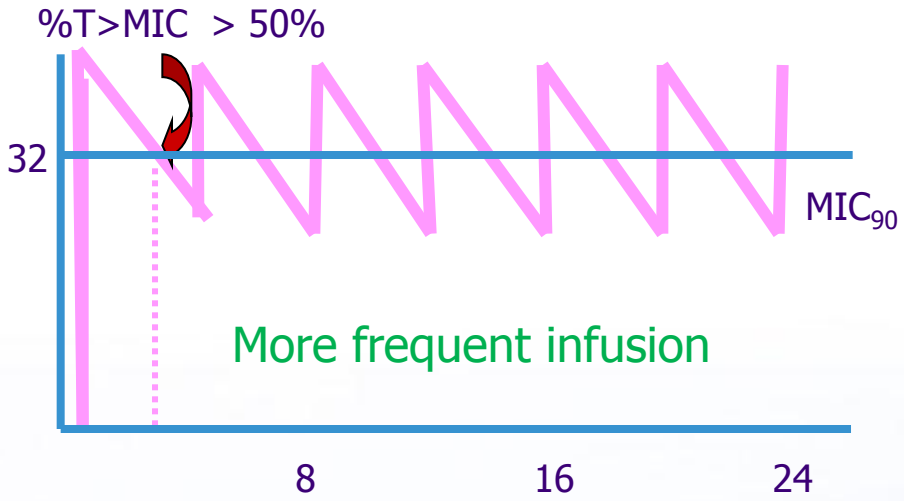
- **Time-dependent antibiotics**
  - Optimal bacterial kill;
    maximum amount of time over the MIC

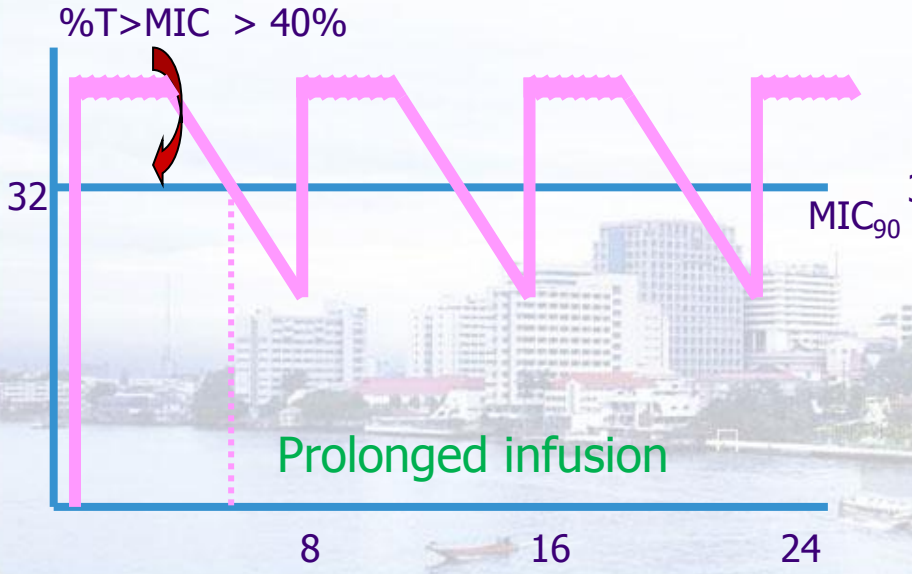
  - Extended or continuous infusions of beta-lactams

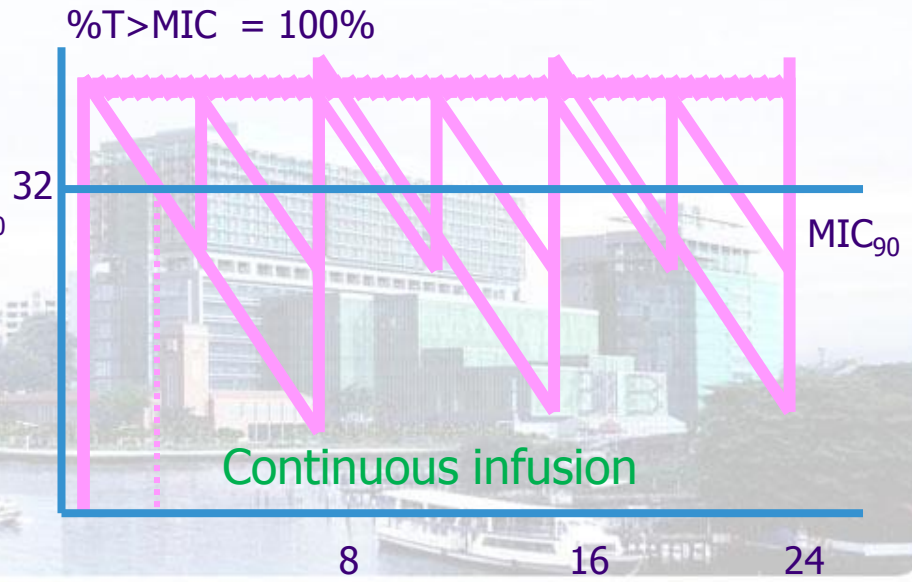
Optimal Antibiotics Administration

Time-dependent









Optimal Antibiotics Administration

- **Time-dependent antibiotics**

Several clinical studies:

- Extended infusion vs standard dosing beta-lactams in the acutely ill patient (include meropenem, piperacillin/tazobactam and doripenem)

- The outcome: varied from no difference in clinical cure in the infusion group to a clinically significant enhanced cure rate

Optimal Antibiotics Administration

- **Time-dependent antibiotics**
- **Glycopeptides: Vancomycin**
  - 100 courses of continuous infusion the treatment of suspected MRSA infections
  - 78%of patients achieved plateau concentrations (>15mg/L) on Day 1 with minimal risk of toxicity (<35mg/L)
  - Increased to 85% on Day 2 sustained for the course
  - The lowest concentration; 9.3 mg/L (> MIC for most MRSA)

Guy's and St Thomas' NHS Foundation Trust (GSTT)

Optimal Antibiotics Administration

Concentration-dependent antibiotics

- **A high initial concentration is required:**
  - Maximum bacterial kill
  - Tissue penetration
- **Aminoglycoside once daily dose**

Optimal Antibiotics Administration

Loading dose (LD)

The LD = V×Cp

the volume of distribution (V)

the required plasma concentration (Cp)

*Hydrophilic agents: which disperse mainly in water

*Lipophilic agents: greater affinity for adipose tissue

Optimal Antibiotics Administration

Hydrophilic agents

- Smaller volume of distribution
- Likely to be renally eliminated unchanged
- Increased clearance in severe sepsis

Beta lactams
Aminoglycosides
Glycopeptides

Lipophilic agents

- Larger volume of distribution
- Likely to be hepatically metabolized
- More likely to penetrate deep tissues

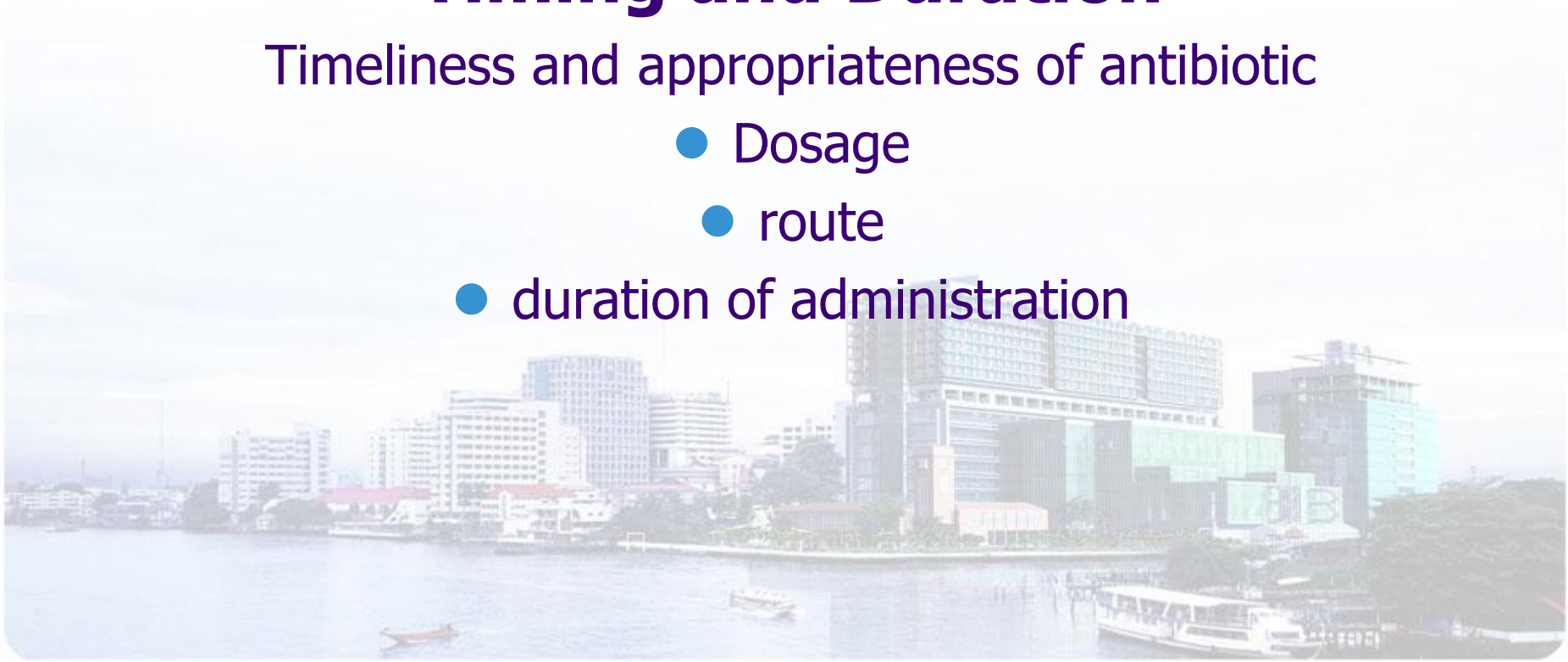
Fluoroquinolones
Macrolides
Rifampicin
Linezolid

Optimal Antibiotics Administration

Appropriate use;
Timing and Duration

Timeliness and appropriateness of antibiotic

- Dosage
- route
- duration of administration



Optimal Antibiotics Administration

- Get effective antibiotic selection, right first time
- Base antimicrobial selection, empiric and targeted; local susceptibility patterns
- Use broad-spectrum "but least" antibiotics early
- Optimize the dose and route of administration
- Administer for the shortest possible duration
- Adjust/stop antibiotic to best target the pathogen(s) and remove pressure for resistance development: de-escalation

Optimal Antibiotics Administration

- **Initiation of antibiotic**
  - Within the first hour after diagnosis of severe sepsis and septic shock

- **Systematic Review and Meta-Analysis The Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis**
  - inappropriate empirical antibiotic treatment is significantly associated with all causes mortality in prospective studies

Optimal Antibiotics Administration

How long should a course of antibiotic therapy last?

- **The Surviving Sepsis Campaign**
  - The duration of therapy should typically be 7–10 days
  - Longer courses may be appropriate if
    - slow clinical response
    - an undrainable focus of infection
    - immunological deficiencies
    - neutropenia

Optimal Antibiotics Administration

How long should a course of antibiotic therapy last?

- **Ventilator-associated pneumonia**
  - Clinical effectiveness was achieved with 8 or 15 d treatment
  - Significant reduction in the emergence of multiresistant pathogens in the shorter course

Optimal Antibiotics Administration

Infection	Minimum duration
VAP	8 days
Pneumococcal meningitis	7 days
Pneumococcal pneumonia	5 days
Empyema/lung abscess	4 - 6 wks
Endocarditis	4 wks
Osteomyelitis	4 wks

Optimal Antibiotics Administration

Organism factors:

- Drug-resistant Gram-Negative Pathogens
- Drug-resistant Gram-Positive Pathogens

MDR bacterial infection

Risk Factors for MDR Pathogens for Both Nosocomial and Community-Acquired Infections

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for health care–associated pneumonia
- Hospitalization for 2 days or more in the preceding 90 days

Adapted from Am J Respir Crit Care Med. 2005;171(4):388-416.

MDR bacterial infection

Risk Factors for MDR Pathogens for Both Nosocomial and Community-Acquired Infections

- Residence in a nursing home or extended care facility
- Home infusion therapy
- Chronic dialysis within 30 days
- Home wound care
- Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Adapted from Am J Respir Crit Care Med. 2005;171(4):388-416.

Optimal Antibiotics Administration

Antibiotics
For
Drug-Resistant GN Infection

Antibiotics For Drug-Resistant GN Infection

- Carbapenem
- Colistin
- Tigecycline
- Combination therapy

Carbapenem

	Ertapenem	Imipenem	Meropenem	Doripenem
I/C	Community settings intraabdominal or skin and soft tissue infection Out patient ATB Rx	Empirical Rx of serious infections in previously multiple ATBs use Polymicrobial infection Suspected MDR or ESBL producer, Amp C producer GNR MDR *P. aeruginosa* infection		
C/I	Relative contraindication to prior hypersensitivity type I to ß lactams			
Dose **loading dose**	1 g IV	1 g IV (> 1 g, epileptogenic)	2 g IV	500 mg (1 g ?) IV
maintenance dose	1 g IV once daily	500 mg-1 g IV q 6 h (max 4 g/d)	1-2 g IV q 8 h (max 6 g/d)	500 mg IV q 8 h (1 g IV q 8 h ?)
prolonged infusion	NA	√ (3 h)	√ (3 h)	√ (3-4 h)
Renal dose adjustment	Yes	Yes	Yes	Yes

Zhanel GG et al. Drugs 2007;67:1027-52, Chahine EB et al. Am J Health-Syst Pharm 2010;67:2015-24, Mandell's Priniciples and practice of infectious disease 7th 2010

Carbapenem

	Ertapenem	Imipenem	Meropenem	Doripenem
Common ADRs	Phlebitis GI upset Rash Pruritus	Phelbitis GI upset Rash Pruritus	Phlebitis GI upset Rash Pruritus	Headache, insomnia GI upset Elevated liver enz. Phlebitis
Epilepto-genicity	Less	0.5-2% Risk factors: renal ds, pre-exisiting CNS ds or infection, Hx of seizure, high dose (≥ 4 g/d)	Less	Less
Special issues	Lowest collateral damage to *P. aeruginosa, A. baumannii*	Intraabdominal infection suspected enterococcal coninfection Resist to imipenem ≠ Resist to meropenem, or doripenem	US FDA approved for Rx of CNS infection	Similar structure to meropenem In *vitro*: MIC90 for *P. aeruginosa* 2-4 times lower than meropenem, but limited clinical data Not substituted to older carbapenems

Zhanel GG et al. Drugs 2007;67:1027-52, Chahine EB et al. Am J Health-Syst Pharm 2010;67:2015-24

Optimal Antibiotics Administration

Carbapenems

- For ESBL and AmpC-producing organisms
- BUT! not for
  - Carbapenem-resistant *P. aeruginosa* and *Acinetobacter* sp.
  - Intrinsically carbapenem-resistant *Stenotrophomonas maltophilia* and *E. faecium*

Polymyxin: Colistin

- **Spectrums:**
  - Some GN *Enterobacteriaceaes*, *A. baumannii*, *P. aeruginosa*
  - Poor activity against *Serratia* spp., *Burkholderia* spp., *Proteus* spp., *Salmonella* spp., *Aeromonas* spp.
  - No activity against GP, most anaerobes

- **Indication**
  Preserved for infection from MDR or pan-DR *A. baumannii*, *P. aeruginosa*, or enterobacteriaceaes

- **Contraindication:**
  polymyxin allergy

Li J et al. Lancet Infect Dis 2006;6:589–601
Mandell's Priniciples and practice of infectious disease 7th 2010

Optimal Antibiotics Administration

Colistin

Adverse effect

- Nephrotoxicity (10% - 20%) : Acute tubular necrosis
- Neurotoxicity (7%) : Dizziness, weakness, facial paresthesia, vertigo, etc.
- Dose dependent & reversible

Risk factors of nephrotoxicity

- Previous renal insufficiency
- Duration of treatment
- Concomitant use of other nephrotoxic drugs

Optimal Antibiotics Administration

Colistin

- Key therapeutic options for carbapenem-resistant organisms ** *P. aeruginosa*, *A. baumannii* and carbapenemase producing *Enterobacteriacae*
- BUT! not for
  - Organisms inherently resistant to polymyxins include *Serratia* sp., *Proteus* sp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Flavobacterium* sp.

Colistin: dose and administration

Suggested Dosing of Colistin based on PK/PD

- **Cr. Clearance > 50 ml/min**

  300 mg, then 150 mg q 12 h or 100 mg q 8 h
- **Cr. Clearance 41 – 50 ml/min**

  300 mg, then 150 mg q 12 h or 75 - 100 mg q 8 h
- **Cr. Clearance 31 – 40 ml/min**

  300 mg, then 75 - 100 mg q 12 h
- **Cr. Clearance 21 – 30 ml/min**

  300 mg, then 75 mg q 12 h or 150 mg q 24 h
- **Cr. Clearance 11 – 20 ml/min**

  300 mg, then 100 mg q 24 h

Thamlikitkul V., Koomanachai P., 2011, unpublished data

Tigecycline

- Derived from minocycline, similar to tetracycline
- Very broad spectrum wtith <u>bacteriostatic activity</u>
  - GP include MRSA, *E. faecalis*, *E. faecium*, and VRE
  - GN include ESBL producing *E. coli*, *Klebsiella* spp., (*A. baumannii*, *Serratia* spp.) *S. maltophilia*
  - Anaerobes, atypical pathogens
  - No activity against *P. aeruginosa*, *Proteus* spp.
- **Contraindication:** hypersensitivity to tetracycline, pregnancy, severe hepatic impairment
- **FDA approved:** cSSSI, cIAI, CAP

Kasbekar N et al. Am J Health-Syst Pharm 2006;63:1235-43

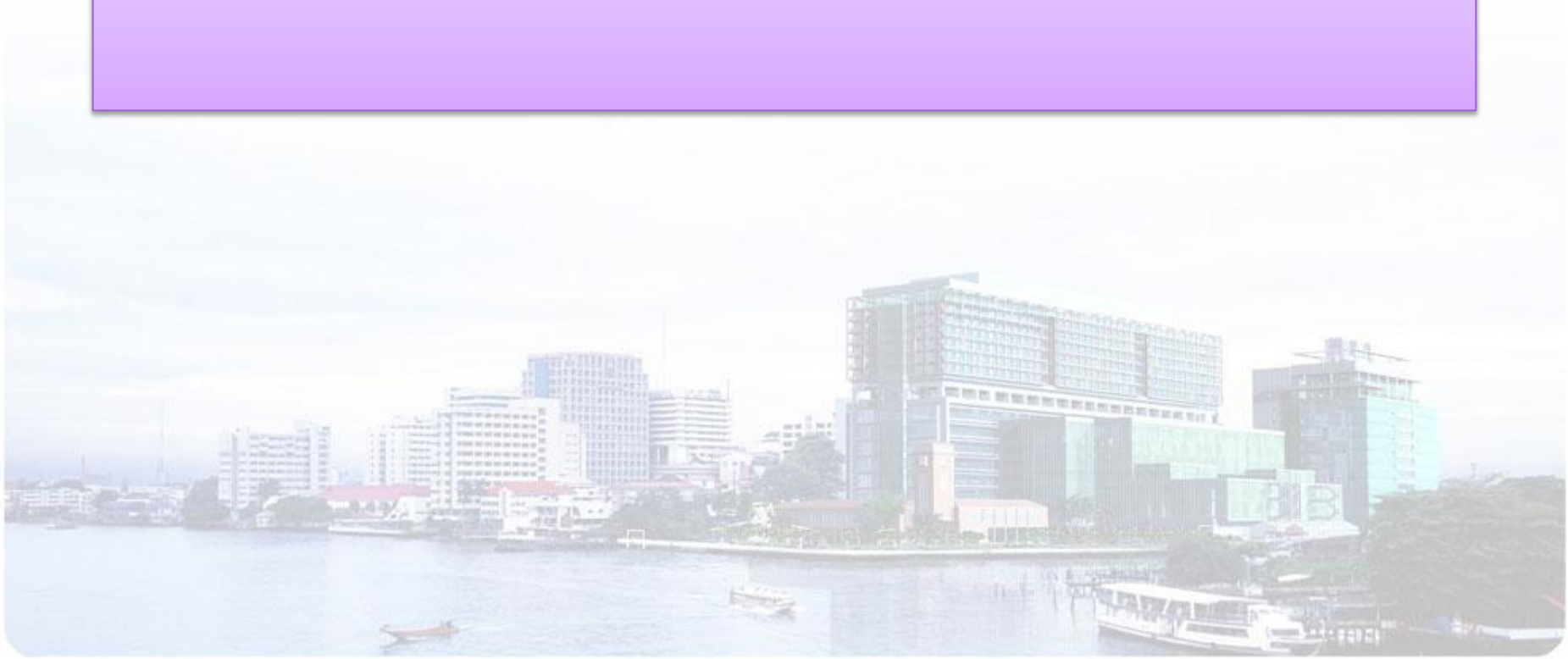
Tigecycline

- **Loading dose:** 100 mg IV infusion 30-60 min
- **Maintenance dose:** 50 mg IV q 12 h
- **Hepatic dose adjustment**
  Severe liver impairment or C-P class C: 100 mg IV loading then maintenance dose 25 mg IV q 12 h
- **Common ADR:** GI disturbance
- **Not recommended: UTI and Bacteremia**

Kasbekar N et al. Am J Health-Syst Pharm 2006;63:1235-43
Peterson LR. International Journal of Antimicrobial Agents 2008;32:S215-22

MDR bacterial infection

Acinetobacter baumannii



Antibiotics against MDR *A. baumannii*

Antibiotics	In vitro activities	Clinical efficacy	Limitation of usage
Colistin	√√	√√	-Nephrotoxicity -Renal dysfunction: dose adjustment
Tigecycline	√√	? Case report or Salvage therapy with colistin	-Low serum concentration -Not enough clinical data
Sulbactam combination	√√	√	-Increasing of resistant
Fosfomycin	√	?	-Not enough clinical data

Antibiotics against MDR *A. baumannii*

Combination therapy

- Insufficient clinical data
- Polymyxins and carbapenems
  (even in the presence of carbapenem resistance)
- Polymixin and tigecycline
- Polymyxin; in vitro synergism together with
  or sulbactam/ampicillin, or rifampicin

Antibiotics against MDR *A. baumannii*

Colistin in Combination Therapy

- Few comparative studies have analysed.
  - No clinical benefits for combination (colistin plus amikacin or β-lactams) therapy in critically ill patients with severe infections by *P. aeruginosa*

Clin Infect Dis 2003;37:e154-60

- No superiority for the association of meropenem-colistin vs colistin alone

Clin Microbiol Infect 2006;12:1227-30

Antibiotics against MDR *A. baumannii*

Colistin in Combination Therapy

- The clinical response in the patients who received colistin alone was 84.8% and in those who received colistin with other antibiotics (aminoglycosides, or carbapenems) was 77.8%

Int J Infect Dis. 2007 Sep;11(5):402-6

- Good response rate (100% of patients, 26/26) from colistin plus rifampicin (10mg/kg q12h) (No control group, limited number of patients)

J Infect 2006;53:274-8

Antibiotics against MDR *A. baumannii*

Aerosolized Colistin

- Adjunct to systemic treatment
- Current published data; too limited to allow determination
- Dosing 75-300 mg/d q 12-24h
- Adverse effect
  - Induce bronchospasm
  - Other minor symptoms:
    cough, sore throat, chest tightness

Crit Care 2005;9:R53-9

Antibiotics against MDR *A. baumannii*

- **Direct instillation of antimicrobial agents into the ventricles**
  - Occasionally necessary in patients
  - Infections that are difficult to eradicate
  - The patient is unable to undergo the surgical components of therapy
  - Must use with intravenous antimicrobial agents

Intrathecal Antimicrobial Agents Administered

Antimicrobial Agent	Daily Intrathecal Dose
Vancomycin	5-20 mg
Gentamicin	1-8 mg
Tobramycin	5-20 mg
Amikacin	5-50 mg
Polymyxin B	5 mg
Colistin	10 mg
Teicoplanin	5-40 mg
Quinupristin/dalfopristin	2-5 mg
Amphotericin B	0.1-0.5 mg

Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)

Antibiotics against MDR *A. baumannii*

Intrathecal colistin administration

- Poorly CSF penetrate
  - CSF colistin concentration is 25% of serum levels, and remained ≥ to the MIC

Eur J Clin Microbiol Infect Dis2002;21:212

- Potentially safe, effective, and treatment option for MDR GNB infection

- Largest series, 51 cases of *A. baumannii* nosocomial meningitis
  - 100% (8/8) of patients treated with intravenous and IT colistin were survived (p = 0.04)

J Antimicrob Chemother 2008;61:908

Antibiotics against MDR A. baumannii

Intrathecal colistin administration

- **Dosing**

  Variable doses ranging from 1.6 to 20 mg/day (q12-48h)

J Infect. 2005;50: 348, J Clin Microbiol. 2005;43:4916, J Antimicrob Chemother. 2004;54:290
J Clin Microbiol. 2000;38:3523 , Clin Infect Dis. 1999;28:916

- **Neurotoxicity**

  - Meningeal irritation; most frequent (20%)
    33% of patients had to be stop treatment
    33% of patients, doses had to be reduced
  - Neurological signs of meningismus with increased cell count in CSF

Int J Antimicrob Agents 2007;29:9-25

MDR bacterial infection

Extended-Spectrum β-Lactamases (ESBL)-producing bacteria

Extended-Spectrum β-Lactamases; ESBL-producing bacteria

- **Hydrolyze**
  - extended-spectrum cephalosporins with an oxyimino side chain
  - oxyimino-monobactam: aztreonam

Cefotaxime
Ceftriaxone
Ceftazidime

- Resistance to these antibiotics and related oxyimino-beta lactams

ESBL-producing bacteria

Enterbacteriaceae spp.: ESBL testing?

Epidemiology

- Latin America 44.0%
- Asia/Pacific Rim 22.4%
- Europe 13.3%
- North America 7.5%

J Antimicrob Chemother 2007;60:1018

Risk factors

- Increasing length of hospital or intensive care unit (ICU) stay
- More severity of clinical status
- Insertion of various types of catheter or devices
- Invasive procedures or surgical interventions
- oxyimino-b-lactams or
- fluoroquinolones,

J of Hosp Infec 2009: 73;345

ESBL-producing bacteria

Treatment of ESBL producing gram-negative bacterial infection

	tro activities	Clinical efficacy
	√√	√√
	X	X
		?
		?
		?
	-/-	?
Colistin	√	?

Cefepime was less effective than imipenem in the clinical studies

-Low serum concentration
-Not enough clinical data

-No clinical data to support

Optimal Antibiotics Administration

Antibiotics
For
Drug-Resistant GP Infection

Antibiotics For Drug-Resistant GP Infection

- Vancomycin
- Fosfomycin
- Linezolid
- Daptomycin
- Tigecycline

Anti-gram positive agents

	Vancomycin	Fosfomycin
Activity	Bactericidal	Bactericidal
Spectrum		
Indication		
Precaution		

Anti-gram positive agents

	Vancomycin	Fosfomycin
Dose and Administration		
Common ADRs		

Anti-gram positive agents

	Linezolid	Daptomycin
Activity	Bacteriostatic	Bactericidal
Spectrum		
Indication		
Precaution		

Perry CM et al. Drugs 2001;61:525-51
Sauermann R et al. Pharmacology 2008;81:79–91
Mandell's Priniciples and practice of infectious disease 7th 2010

Anti-gram positive agents

	Linezolid	Daptomycin
Dose and Administration		
Common ADRs		

Perry CM et al. Drugs 2001;61:525-51
Sauermann R et al. Pharmacology 2008;81:79–91
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MDR bacterial infection

Enterococcus spp.

Enterococcal infection

- **Risk factors**

  - cystoscopy
  - cesarean section
  - prostatectomy
  - transrectal prostatic biopsy
  - transjugular intrahepatic portosystemic shunt (TIPS)
  - extracorporeal shock wave lithotripsy
  - colonoscopy
  - fiberoptic sigmoidoscopy liver biopsy

- **The infection usually originates from**

  - The genitourinary or gastrointestinal tract
  - Procedures associated with the development of enterococcal endocarditis
  - Malignant and inflammatory lesions of the gut and biliary tract may also be the source of endocarditis

Clin Microbiol Rev 1990; 3:46-65
Medicine (Baltimore) 2007; 86:363-377
Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)

Vancomycin-Resistant *Enterococcus* (VRE)

Risk factors for VRE colonization and infection

- Prolonged hospital stays
- Exposure to intensive care units
- Post-transplantation
- Hematologic malignancies
- Exposure to antibiotics
  - Vancomycin
  - The extended-spectrum cephalosporins**
  - Antibiotics with potent activity against anaerobic bacteria

Antibiotics against *Enterococcus* spp.

Antibiotics	*E. faecalis*	*E. faecium*	VRE
Penicillin	+	+ /-	-
Ampicillin	+	+	+/- (if suscept.)
Pip/Tazo	+	+/-	-
Imipenem	+	+/-	-
Meropenem	+/-	-	-

Microbiology (2009), 155, 1749-1757
Emerg Med Clin N Am 2008; 26:813-834
Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)

Antibiotics against *Enterococcus* spp.

Antibiotics	*E. faecalis*	*E. faecium*	VRE
Aminoglycoside	+	+ (gentamicin)	+ (if suscept.)
Vancomycin	+	+	-
Linezolid	+	+	+ (bacteriostatic)
Daptomycin	+	+	- (not approved by FDA)
Tigecycline	+	+	+/- (limited clinical data)

Microbiology (2009), 155, 1749-1757
Emerg Med Clin N Am 2008; 26:813-834
Mandell, et al. Principles and Practice of Infectious Diseases, 7th Ed(2010)

Important messages

Factors influencing antimicrobial use……

- **Consideration of drugs**
  - Dose and route of administration result in adequate drug level at the site in sufficient period
  - Have bactericidal activity against the pathogenic organism
- **Consideration of organisms**
  - MDR
  - Clinical data evidence
- **Consideration of host and site of infecton**
  - Local factors at the site
  - Host defenses/host factors
  - Adjunctive therapies : remove foreign body, drainage, immunomodulation, etc

Thank You !