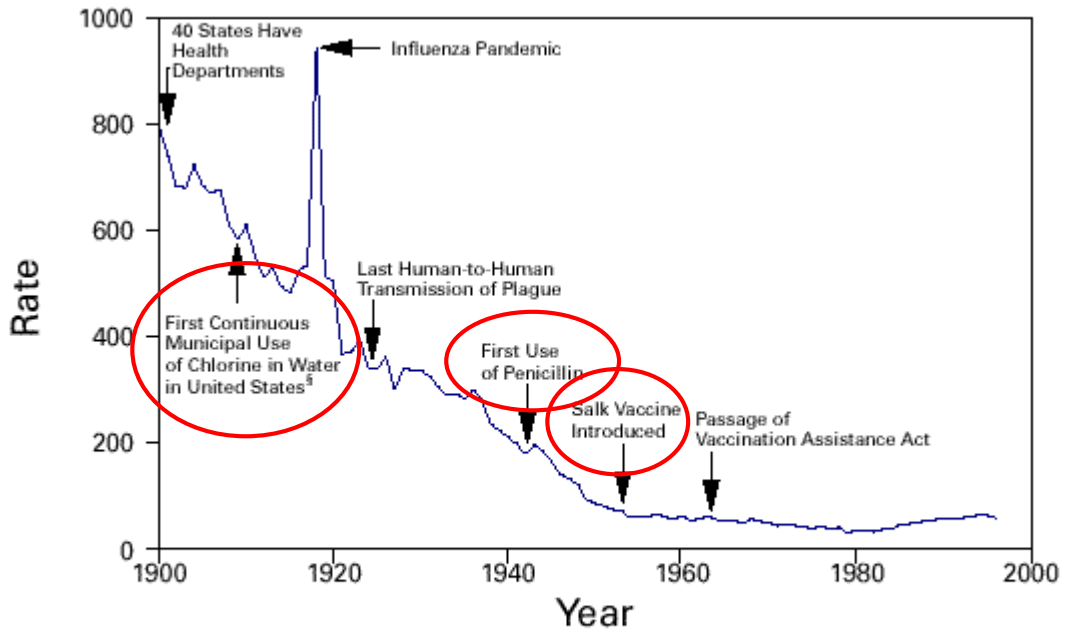
ANTIBIOTICS IN CRITICALLY ILL PATIENTS
CLINICAL PHARMACOLOGY

Lenka Součková

Control of infectious disease

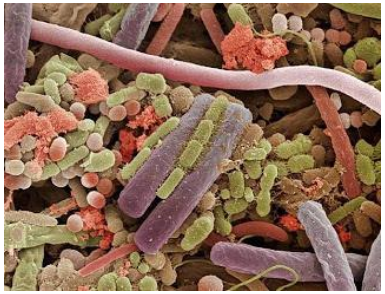
FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†



*Per 100,000 population per year.
†Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999:281;61–6.
§American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

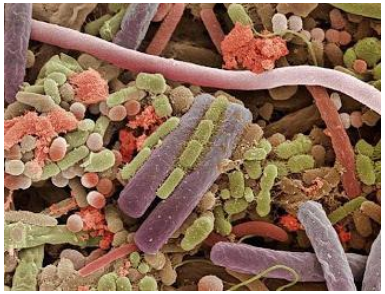
MMWR, Achievements in Public Health, 1900-1999: Control of Infectious Diseases, 1999 / 48(29);621-629

Great antibiotic



Pathogen → Clear solution → Cure the patient

Is always ATB great?

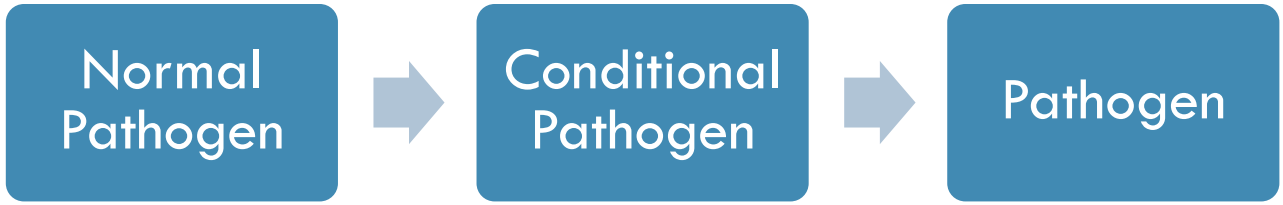


Pathogen → Clear solution ✗ Cure the patient

Critical steps in antibiotic therapy

- Determine
  - the right time initiating antibiotic therapy - golden hour of sepsis
  - ATB selection
  - the correct dose - dose optimisation - iv to oral switch
  - the correct time interval
  - duration of antibiotic therapy - de escalation
  - inappropriate or redundant antibiotics (dual anaerobic cover etc)
- Recognize different types of ADRs of individual antibiotics and suitably replace
- Identify where the use of antibiotics inappropriate / unwanted

Normal flora



- Microbes that engage in mutual or commensal associations - **normal (resident) flora,** indigenous flora, microbiota
- **Infection**- a condition in which pathogenic microbes penetrate host defenses, enter tissues and multiply
- **Disease** – any deviation from health, disruption of a tissue or organ
- Caused by microbes or their products – **infectious disease**

Table 21.1 **Representative genera of microorganisms in the normal flora of humans**

Anatomical site	Genera[a]
Skin	*Acinetobacter, Corynebacterium, Enterobacter, Klebsiella, Malassezia (f), Micrococcus, Pityrosporum (f), Propionibacterium, Proteus, Pseudomonas, Staphylococcus*
Mouth	*Streptococcus, Lactobacillus, Fusobacterium, Veillonella, Corynebacterium, Neisseria, Actinomyces, Geotrichum (f), Candida (f), Capnocytophaga, Eikenella, Prevotella,* spirochetes (several genera)
Respiratory tract	*Streptococcus, Staphylococcus, Corynebacterium, Neisseria, Haemophilus*
Gastrointestinal tract	*Lactobacillus, Streptococcus, Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Clostridium, Escherichia, Klebsiella, Proteus, Enterococcus, Staphylococcus*
Urogenital tract	*Escherichia, Klebsiella, Proteus, Neisseria, Lactobacillus, Corynebacterium, Staphylococcus, Candida (f), Prevotella, Clostridium, Peptostreptococcus, Ureaplasma, Mycoplasma, Mycobacterium, Streptococcus, Torulopsis (f)*

[a] This list is not meant to be exhaustive, and not all of these organisms are found in every individual. Some organisms are more prevalent at certain ages (adults vs. children). Distribution may also vary between sexes. Most of these organisms can be opportunistic pathogens under certain conditions. Several genera can be found in more than one body area. (f)–fungi.

Table 21-1 Brock Biology of Microorganisms 11/e

Symbiosis, natural protection

Eradicate all pathogen

NONSENSE

Innate Resistance to Infection

- Nonspecific physical, anatomical, and chemical barriers prevent colonization of the host by most pathogens
- Lack of these defenses results in susceptibility to infection and colonization by a pathogen.
  - Anatomic barriers breached (IV's, foleys, vents etc.)
  - Exposure to virulent pathogens
    - many resistant to multiple antibiotics

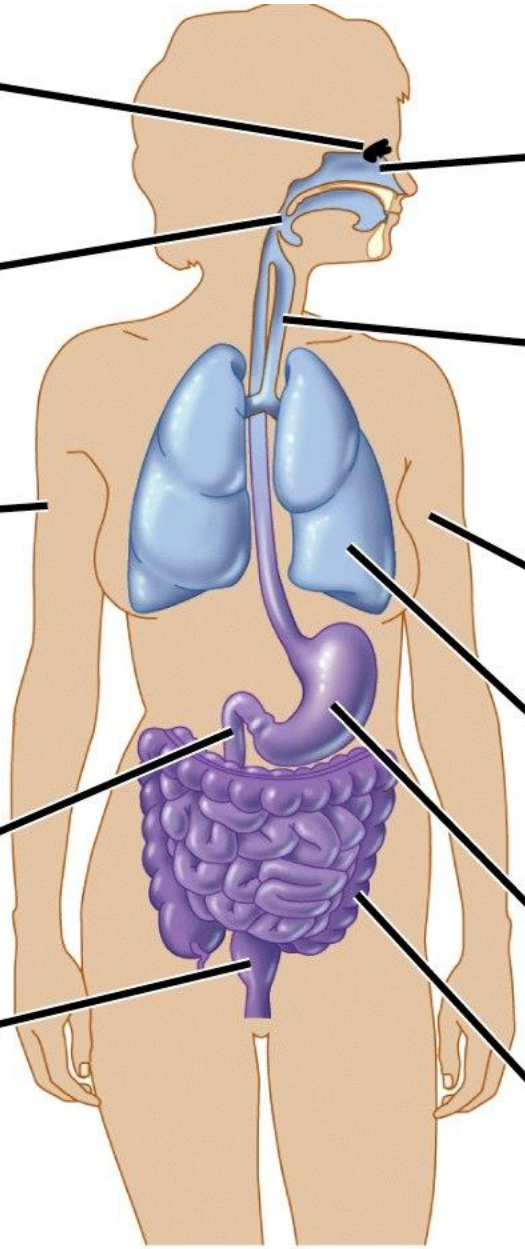
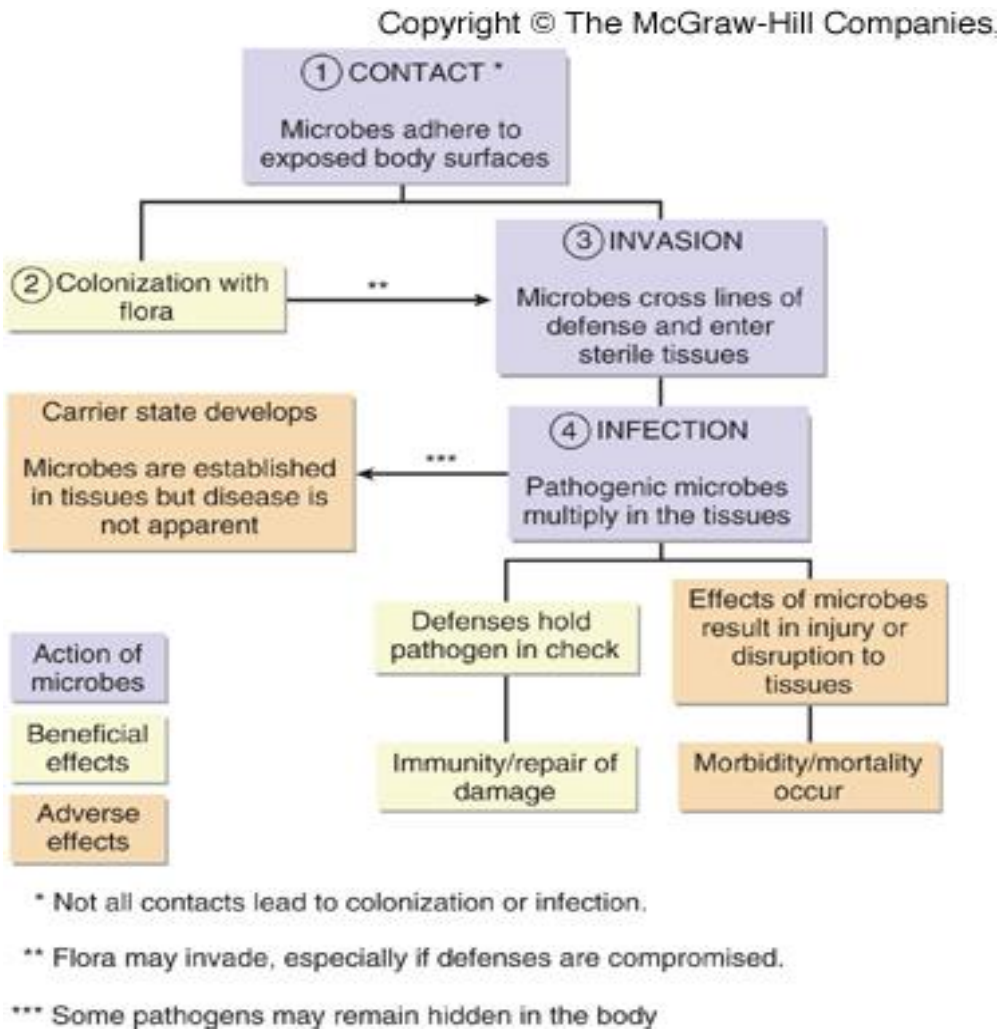


Figure 21-24 Brock Biology of Microorganisms 11/e

Innate Resistance to Infection



Innate Resistance to Nosocomial Infection

- Many hospital patients with noninfectious diseases (for example, cancer and heart disease) acquire microbial infections because they are compromised hosts.
- Host defenses depressed by underlying disease or treatment, malnutrition, age
- Such hospital-acquired infections are called **nosocomial** infections.

Where do the microbes come from?

- patient's own flora
- cross infection from medical personnel
- cross infection from patient to patient
- hospital environment- inanimate objects
  - air
  - dust
  - IV fluids & catheters
  - washbowls
  - bedpans
  - endoscopes
  - ventilators & respiratory equipment
  - water, disinfectants etc

The Inanimate Environment Can Facilitate Transmission

~ Contaminated surfaces increase cross-transmission ~

Abstract: The Risk of Hand and Glove Contamination after Contact with a VRE (+) Patient Environment. Hayden M, ICAAC, 2001, Chicago, IL.

SOURCES OF PATHOGENS IN NI

- **Reactivation of latent infection:** TB, herpes viruses
  - Less common
- **Endogenous:** normal commensals of the skin, respiratory, GI, GU tract
  - common
- **Exogenous**
  - **Inanimate environment: *Aspergillus* from hospital construction, *Legionella* from contaminated water**
  - **Animate environment: hospital staff, visitors, other patients**
    - **Cross transmission- common**

Site of infections

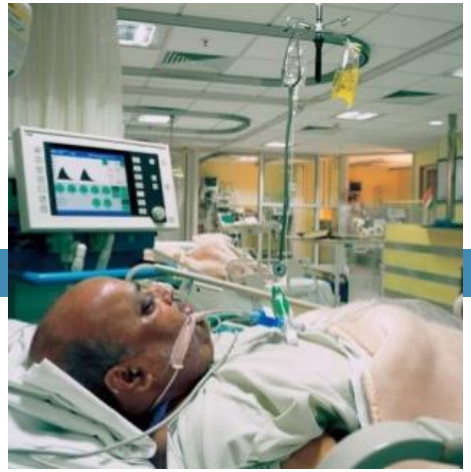
- Pathogen invasion starts at the site of adherence and may spread throughout the host via the circulatory systems.
  - 4 major nosocomial infections:
  - UTI, VAP, SSI, BSI

- Urosepsis 40% - Urinary tract
- Pneumonia 20% - Lung
- Surgical site 17%
- Bloodstream (IV) 8% - catheter infections

  - GIT – *salmonela, clostridum diff.*
  - infections in the abdominal cavity
  - meningitis
  - bacterial endocarditis
  - localized infections, abscesses and other

SEPSIS

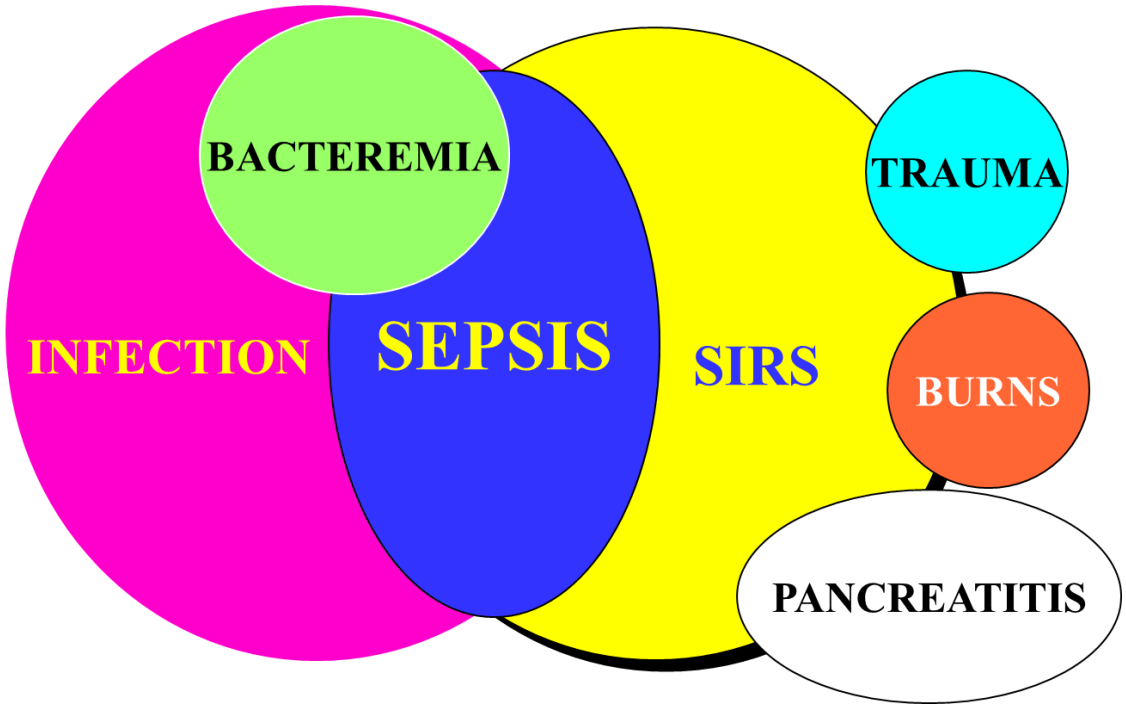
Sepsis



- Sepsis, severe sepsis and septic shock remains a major cause of morbidity and mortality
- Mortality for severe sepsis ≥5-fold higher than that for acute coronary syndrome or for stroke.
- Incidence of sepsis requiring intensive care admission of 0.25–0.38 per 1000 population, suggesting ~2 million admissions to critical care units alone.
- The EPIC study, a point prevalence study performed in 1265 critical care units in 2009 evaluated 14414 patients estimated that over half the patients in the units were infected, more than 70% of them were on antibiotics and 62% of the microbiological isolates were gram negative bacteria.

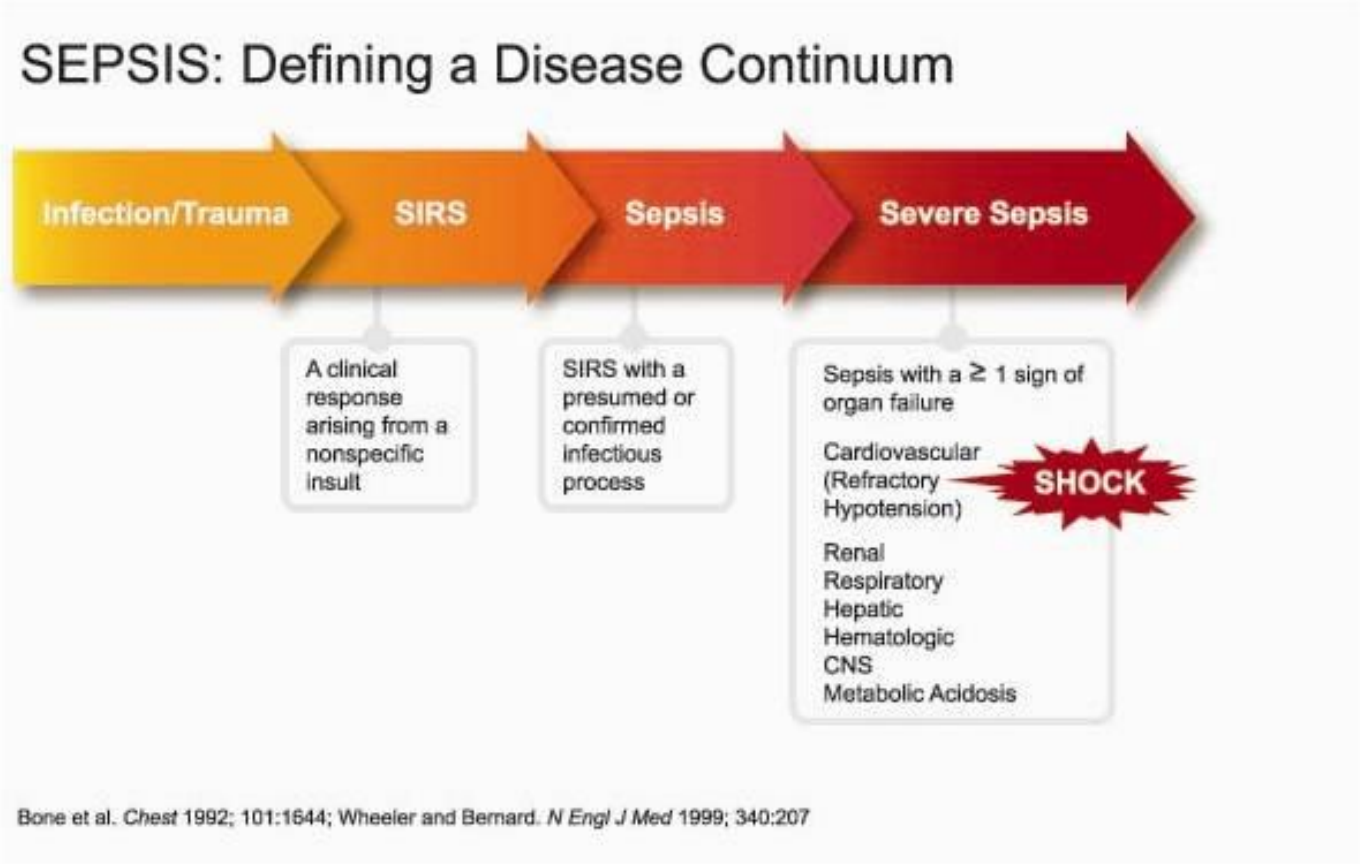
Objectives

- Define SIRS / sepsis / severe sepsis / septic shock
- Early recognition of Sepsis
- Early Goal Directed Therapy



Definitions

- A continuum of severity describing the host systemic inflammatory response



SIRS

- SIRS – systemic inflammatory response syndrome
- Must have at least 2 of the following:
  - **Temperature >38.5°C or <36°C**
  - **Heart rate >90 beats/min**
  - **Respiratory rate >20 breaths/min or PaCO2 <32 mmHg**
  - **WBC >12,000 cells/mm3, <4000 cells/mm3, or >10 % immature (band) forms**
- SIRS is the body's response to infection, inflammation, stress.

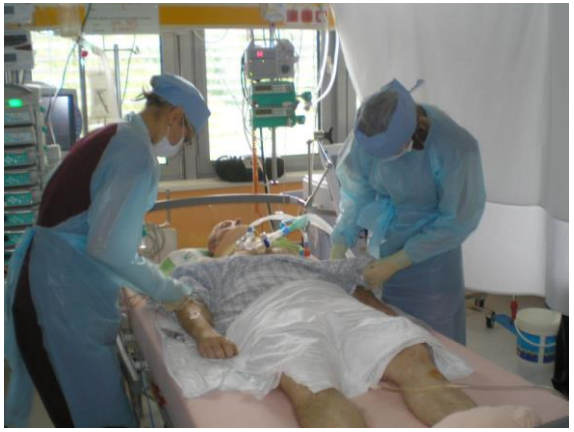
Sepsis and Severe Sepsis

- Sepsis – SIRS + suspected or confirmed infection (documented via cultures or visualized via physical exam/imaging)
- Severe Sepsis – Sepsis + at least one sign of organ hypo-perfusion or dysfunction

Areas of mottled skin	Disseminated intravascular coagulation
Capillary refill > 3 secs	AKI
UOP < 0.5cc/kg /hr	ARDS or acute lung injury (ALI)
Lactate > 2mmol /L	Cardiac dysfunction on echo
Altered mental status	Plt < 100
Abnormal EEG	Troponin Leak

Septic Shock

- Septic Shock - Severe sepsis plus one of the following conditions:
  - MAP <60 mm Hg (<80 mm Hg if previous hypertension) after adequate fluid resuscitation
  - Need for pressors to maintain BP after fluid resuscitation
  - Adequate fluid resuscitation = 40 to 60 mL/kg saline solution (NS 5L-10L)
  - Lactate > 4mmol /L



Antibiotics

- Cultures / Antibiotics / Labs
  - Cultures PRIOR to Antibiotics (2 Sets, one peripheral and one from any line)
  - IV Abx within 1 hr in the ICU
    - Broad Spectrum, combination therapy for neutropenic and patients with pseudomonas risk factors
- Consider need for Source Control !
  - Drainage of abscess or cholangitis, removal of infected catheters, debridement or amputation of osteomyelitis

Fluid therapy

- Central Line Access (Fluid hydration +/- pressor)
- 1st line therapy – fluids, fluids, fluids!
- Crystalloid equivalent to colloid
- Initial 1-2 Liters (20mg /kg) crystalloid or 500 ml colloid
- Careful in CHF patients !!

Pressors

- See separate lecture on vasopressors
  - Start with norepinephrine as first line therapy +/- Vasopressin
  - Consider Dopamine peripherally on floor
    - ** This is available in crash cart ** If not responding to fluids, don't want for pharmacy to send levophed.

Corticosteroids

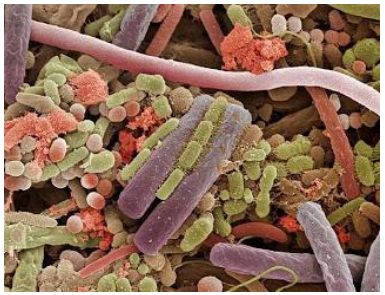
- Use in Septic Shock, if NO response to vasopressors and fluids
  - HYDROCORTISONE 200mg -300mg / day Divided doses (Q6hrs)
    - Initial Dose 100mg IV x1
    - Consider for patients who received etomidate
    - No need for cosyntropin stim test
    - Wean Steroids QUICKLY once off pressors

KEY TAKE HOME POINTS

- Recognize Sepsis EARLY and determine SEVERITY
- EARLY Antibiotics are critical to resolution of shock
- RESUSCITATE severe sepsis and septic shock ASAP
- EARLY GOAL DIRECTED THERAPY

Antibiotics therapy

Pharmacokinetics and Pharmacodynamics as steps leading to optimalization of ATB treatment



Pathogen → Great and clear solution → PK/PD → Succesfull treatment

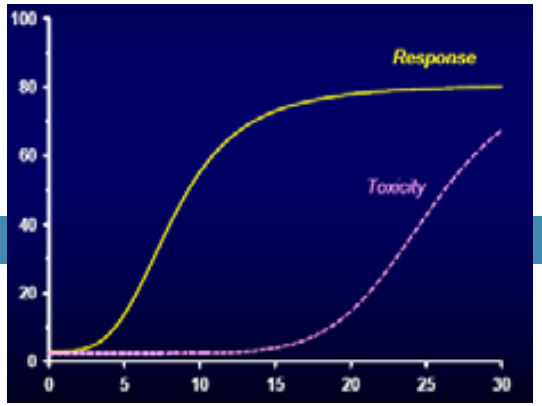
Therapeutic failure, definition and causes

Table III. Causes of low level of antibacterial exposure in the infection focus

Administration of insufficient doses
Poor tissue penetration
Increase in interstitial extracellular fluid volume
Increase of oedema (third space)
Rapid fluid infusion
Pleural effusion
Ascites
Hypoalbuminaemia
Massive postoperative drain losses
Increased plasma clearance or glomerular hyperfiltration
Burn patients (>30–40%)
Clinical conditions associated with hyperdynamia (severe sepsis, polytrauma)
Use of haemodynamically active drugs (vasoactive drugs, diuretics)
Acute haematological diseases (leukaemia)
Consumers of drugs of abuse

Drugs 2012; 72

PK/PD princip



Dose of ATB
A
D
M
E

Plasma concentration changing in time

Concentration in non targeted site

Toxicity

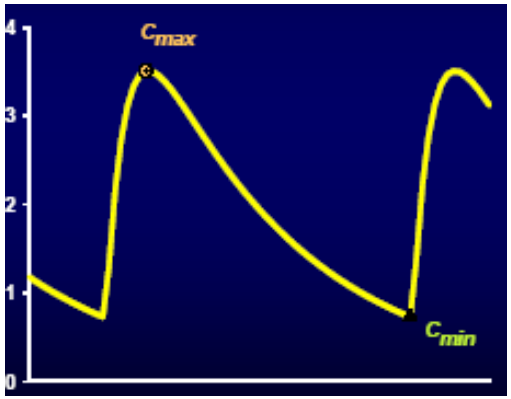
MIN

Concentration in action site

Therapeutic effect

MAX

Protein binding,
Cmax, Cmin,
Half-life,
AUC,
Tissue,
Distribution



W.A. Graig

PK/PD properties of ATB

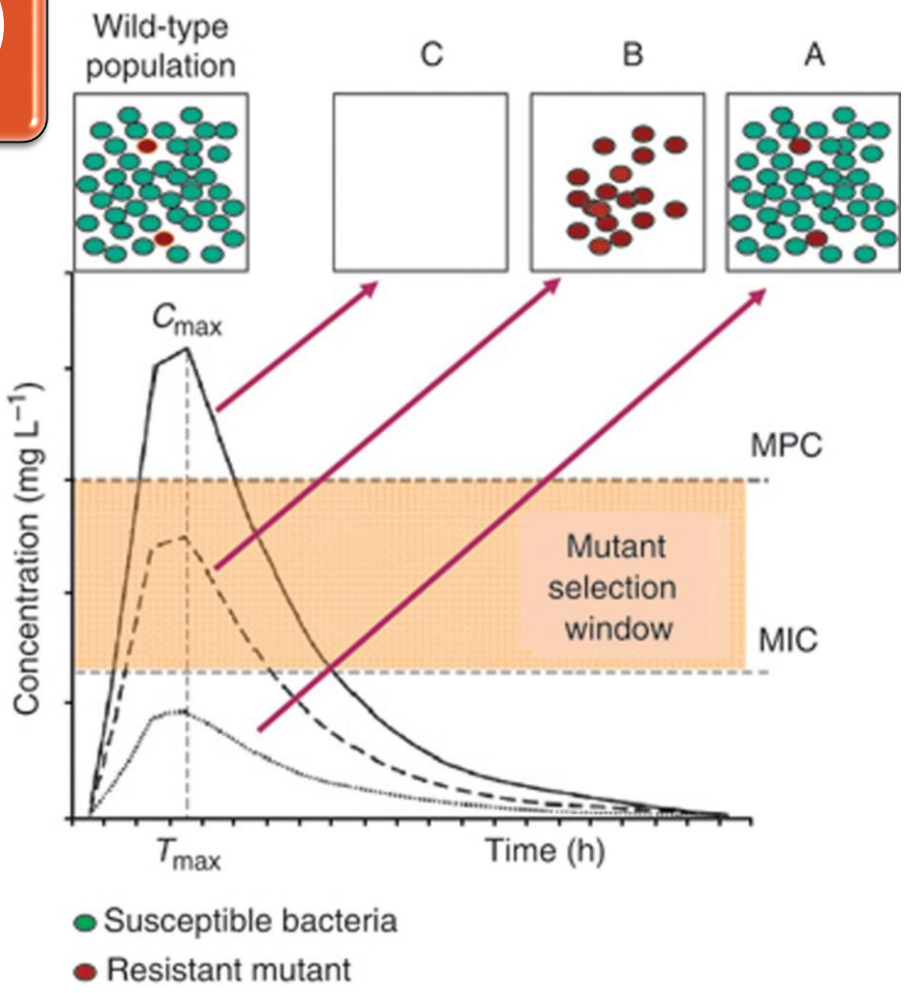
C (max) Peak

AUC

C (min)

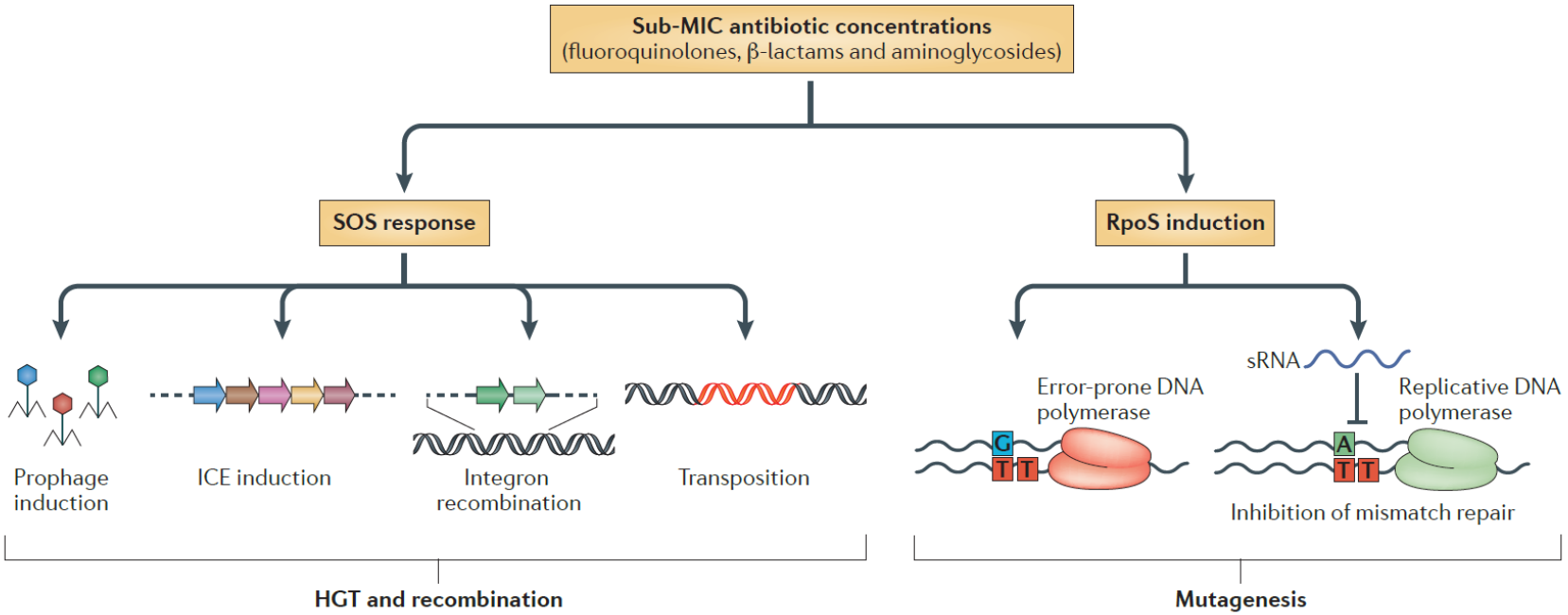
Plasma concentration changing in time

Plasma concentration of ATB defines the ATB effect



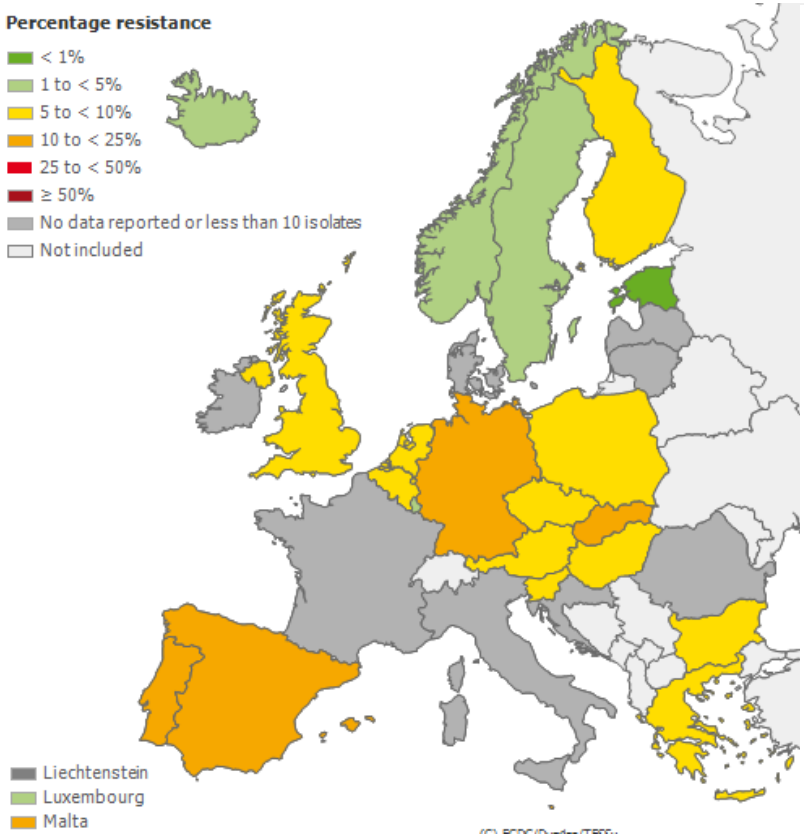
Emergence and spread of antibiotic resistance following exposure to antibiotics
Rafael Cantón , María-Isabel Morosini
FEMS Microbiology Reviews Sep 2011, 35 (5) 977-991; DOI: 10.1111/j.1574-6976.2011.00295.x

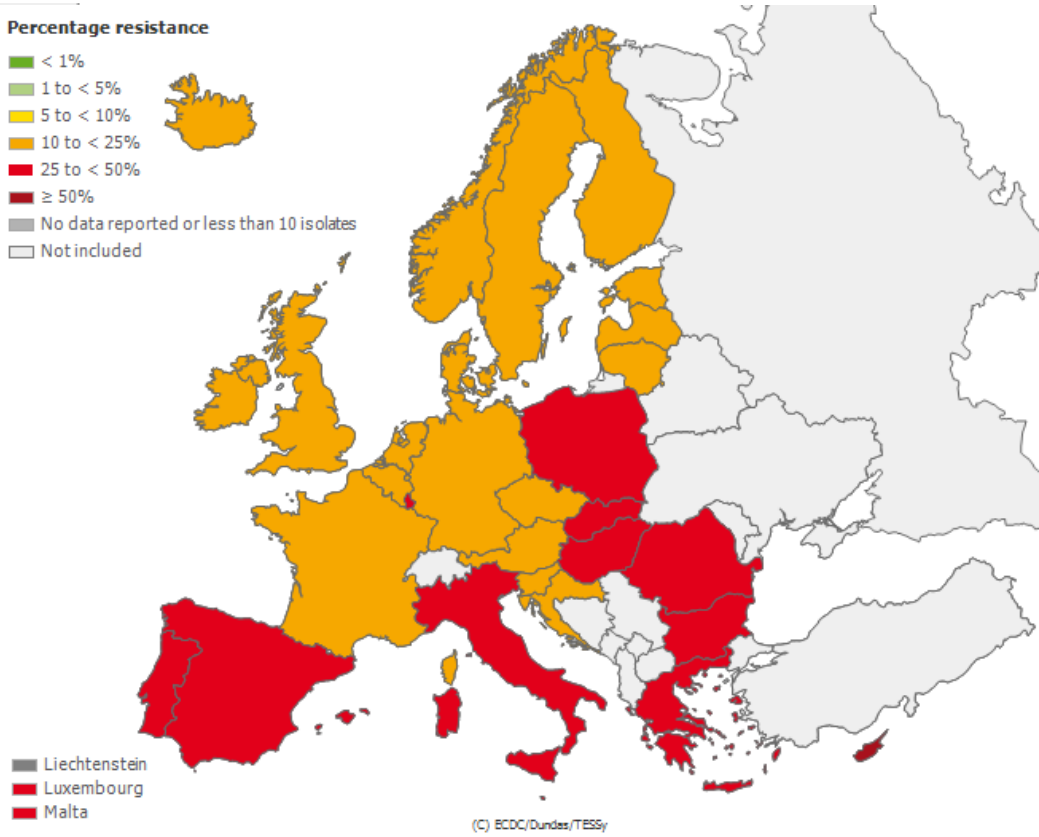
The phenomenon of acquired resistance



Andersson DI. Nature Reviews Microbiology 12.7 (2014): 465-478.

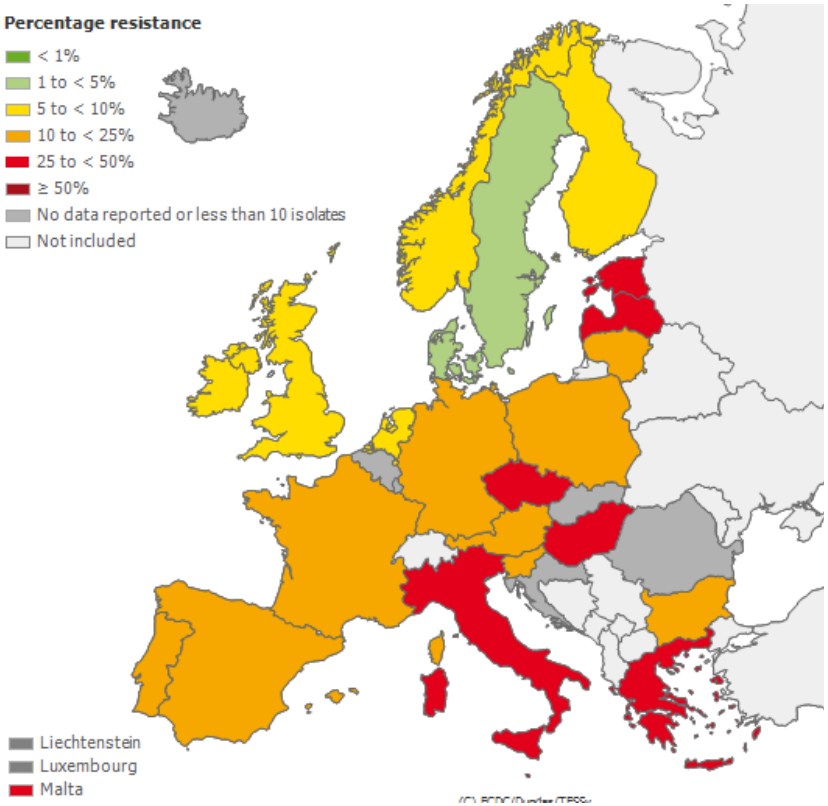
Escherichia coli and fluoroquinolones



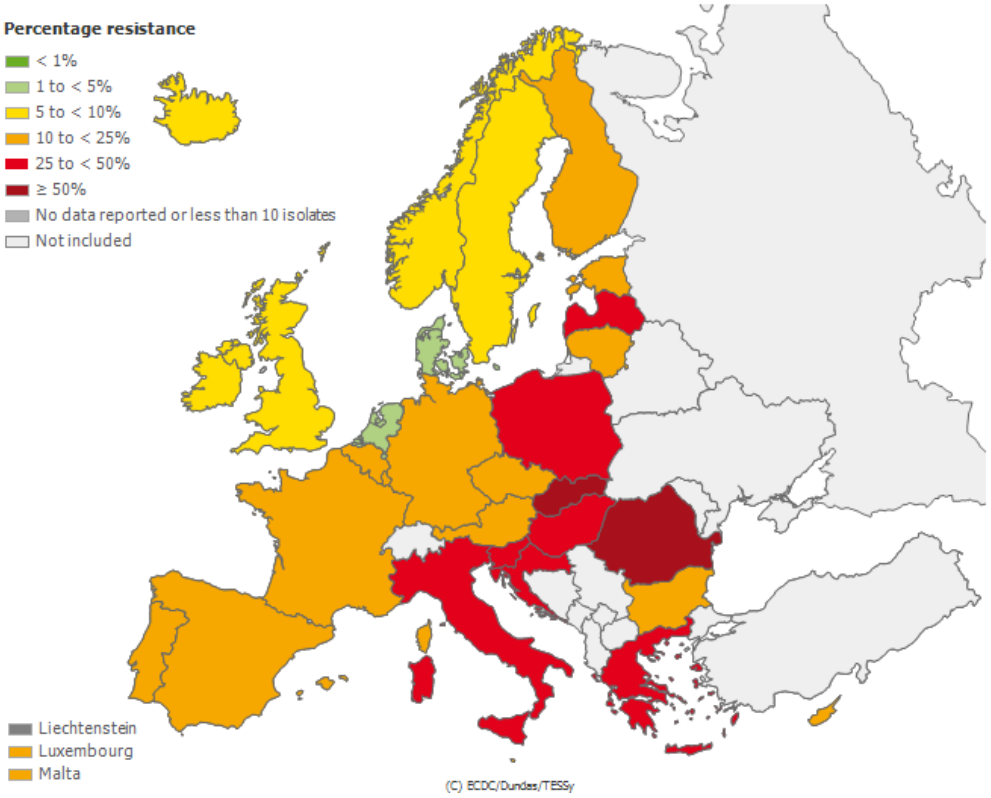


http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

Pseudomonas aeruginosa – *carbapenems* databáze EARS-Net



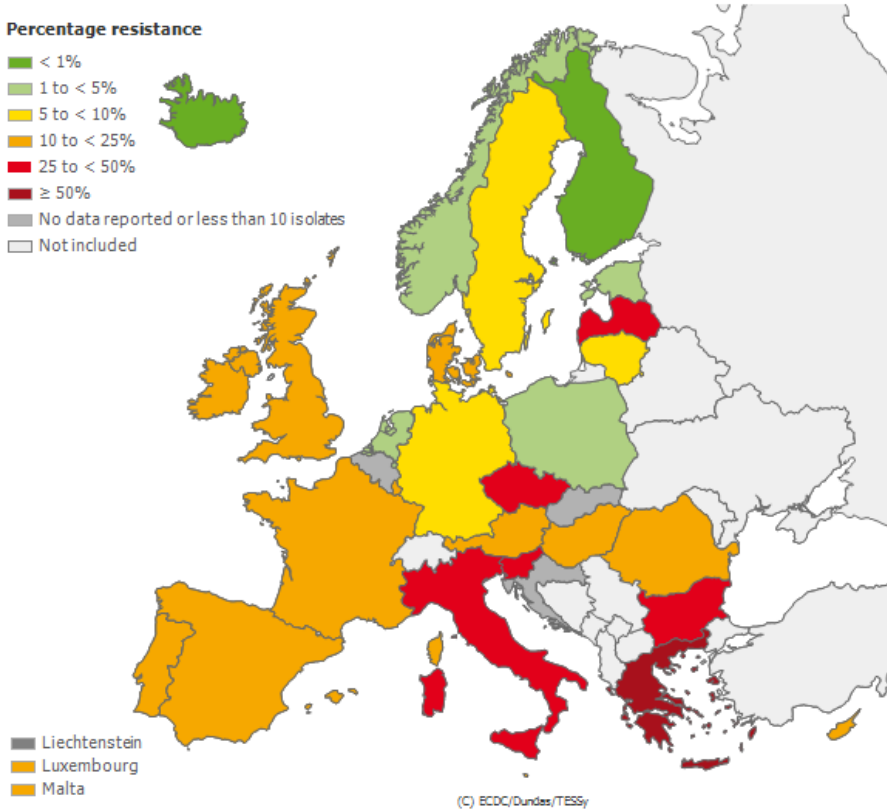
2008



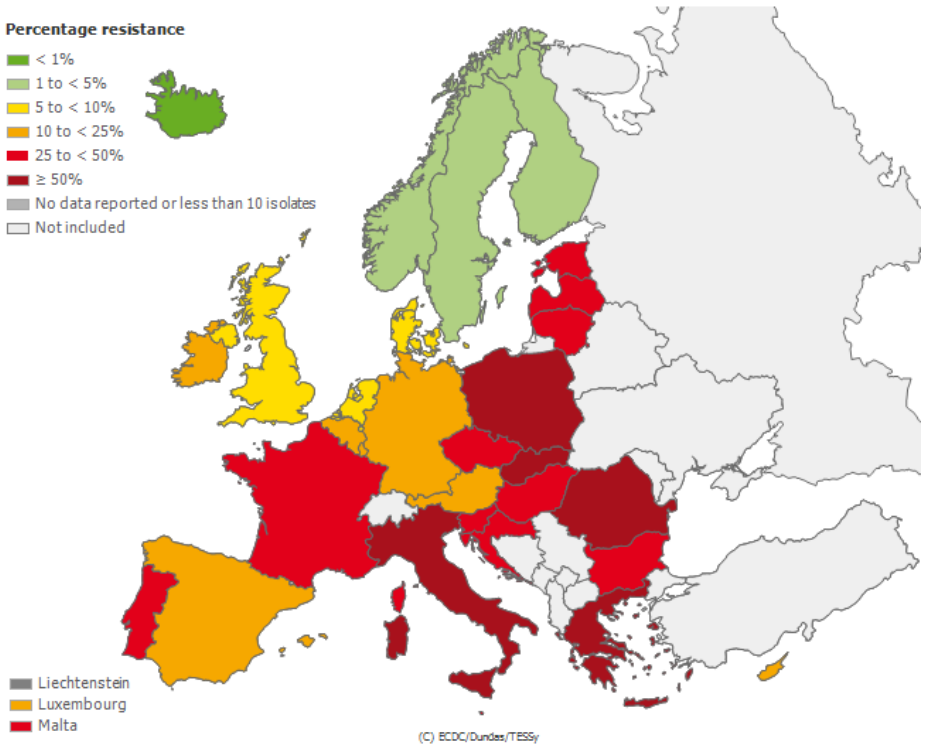
2013

http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

Klebsiella pneumoniae and fluoroquinolones



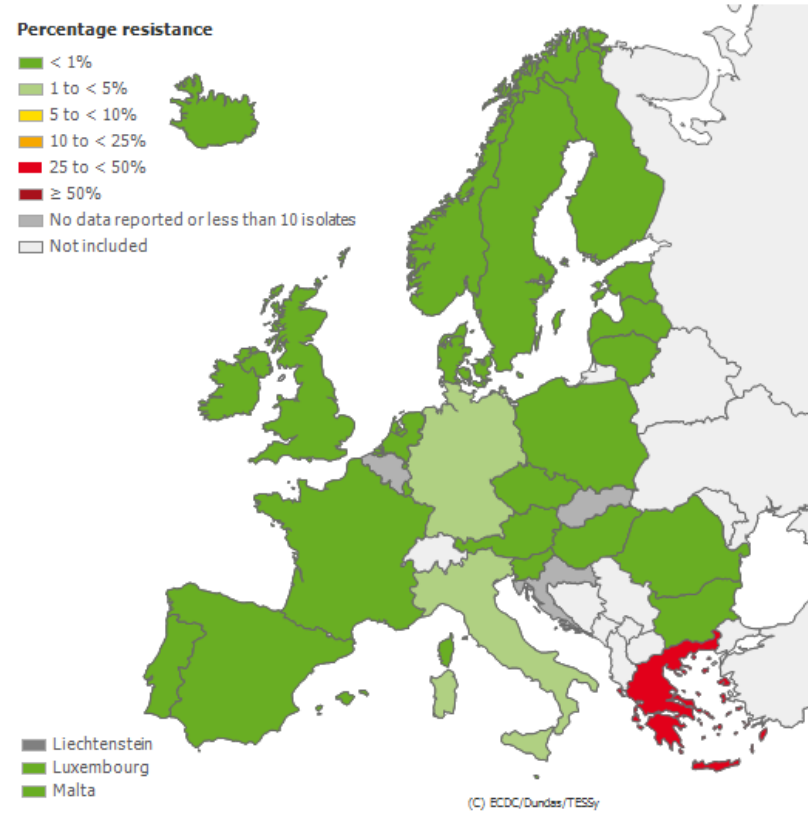
2007



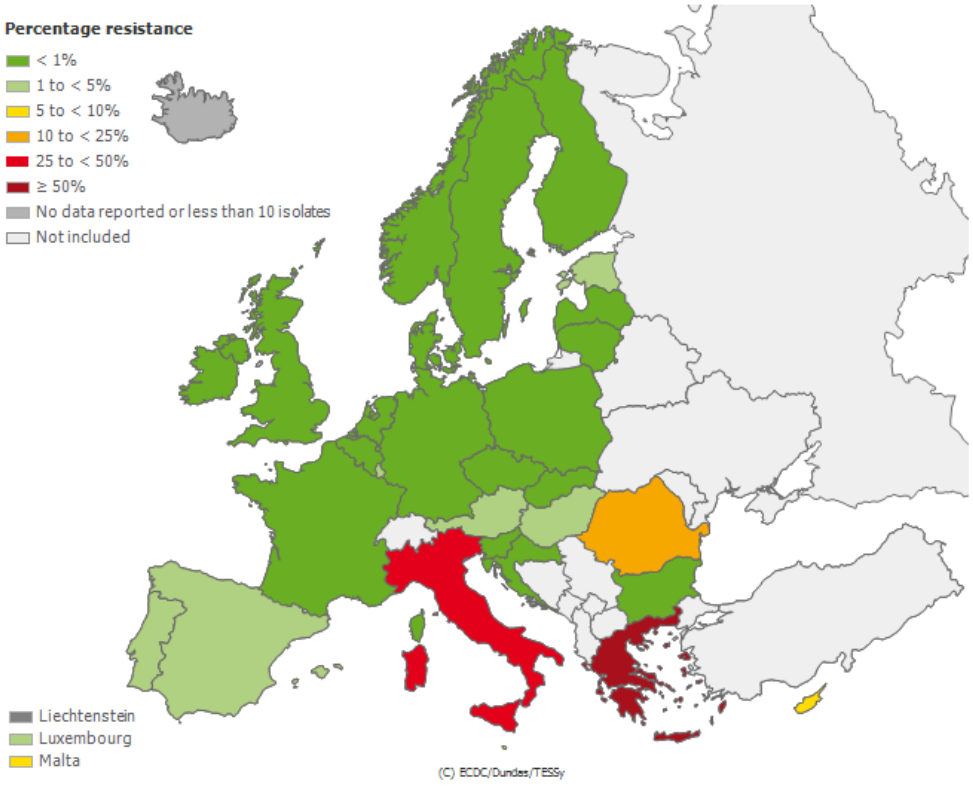
2013

http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

Klebsiella pneumoniae – carbapenems database EARS-Net



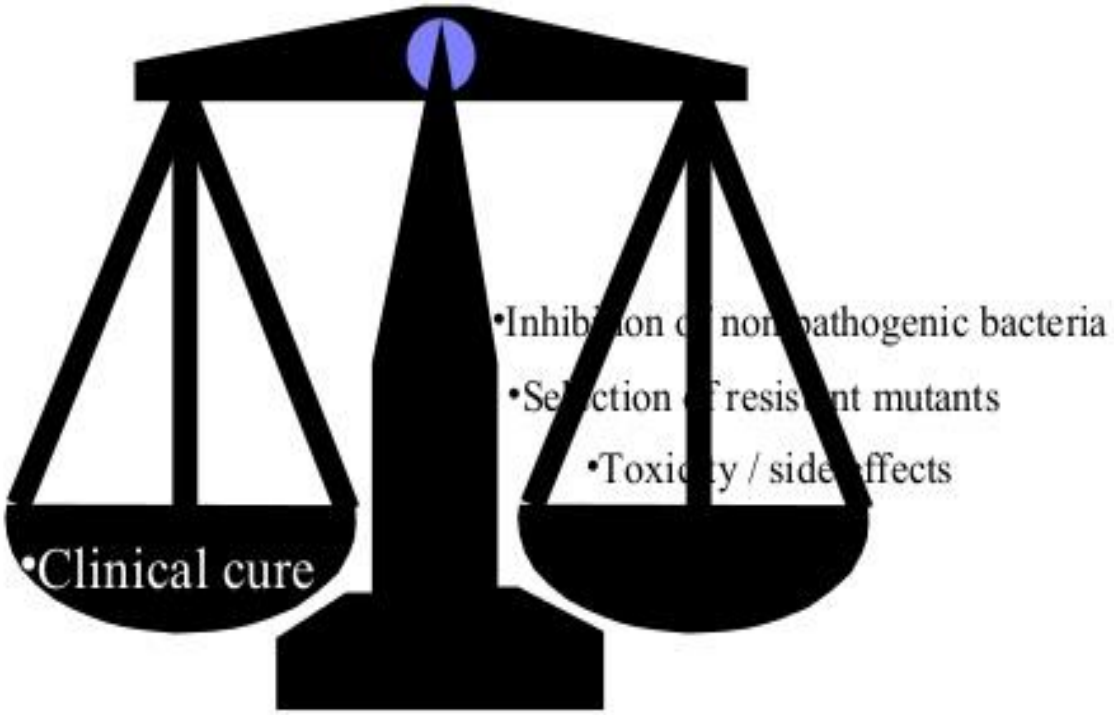
2007

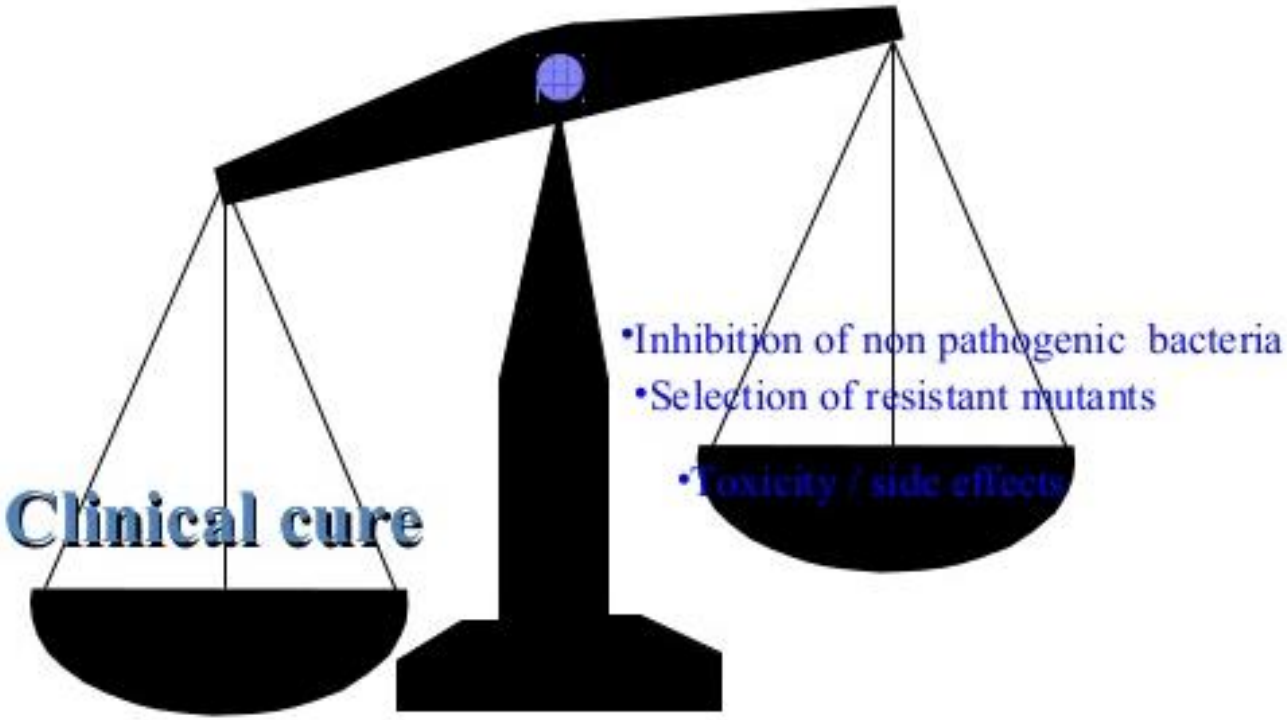


2013

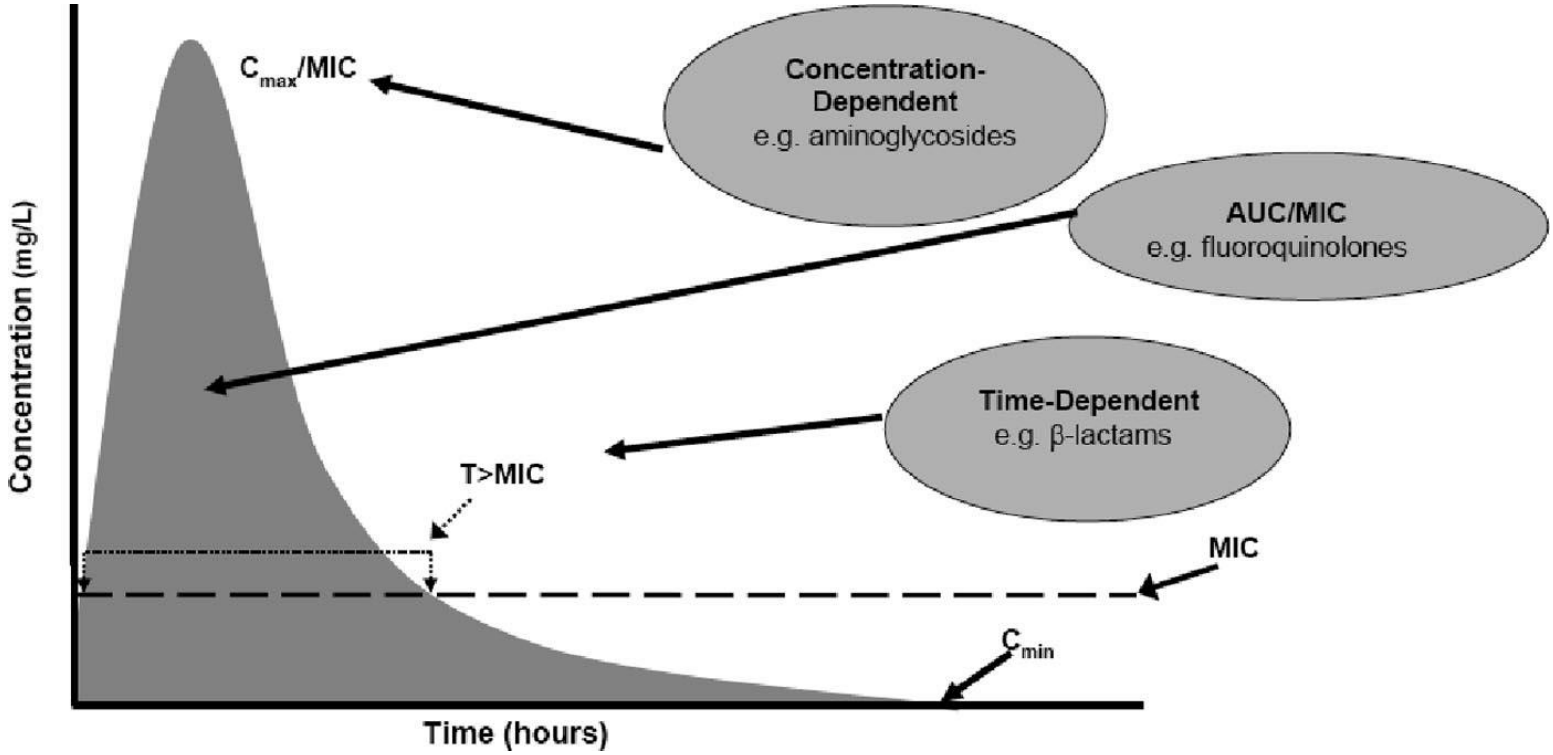
http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

Consequences of antibiotic use




Clinical cure
•Inhibition of non pathogenic bacteria
•Selection of resistant mutants
•Toxicity / side effects

PK and PD parameters of ATBs on a concentration vs. time curve



Key:

T >MIC—The time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period;

Cmax/MIC, the ratio of the maximum plasma antibiotic concentration (C max) to MIC;

AUC/MIC, the ratio of the area under the concentration time curve during a 24-hour time period (AUC0–24) to MIC.

Roberts JA, Crit Care Med 37 (3) 2009

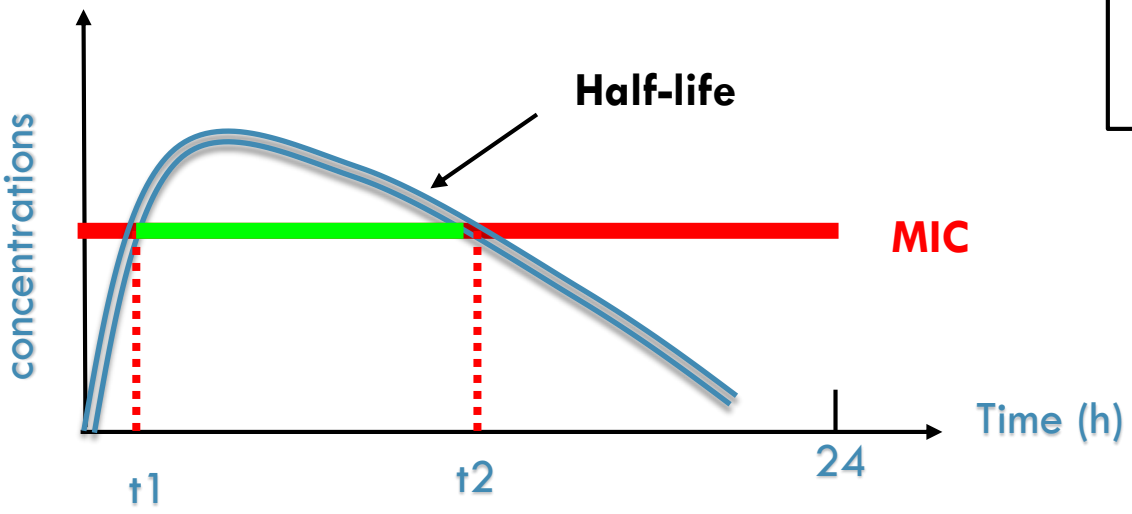
Pharmacodynamic properties that correlate with efficacy of selected antibiotics

PK/PD characteristics	Time>MIC	24h AUC/MIC	Cmax/MIC
Antibiotics	β Lactams Carbapenems Linkosamids Klindamycine Vancomycine	Quinolones Tetracyclines Glykopeptidy Linezolid	Aminoglycosides Metronidazole
Target	Maximizing time of ATB exposure	Optimization of the ATB dose administered over time	Optimalization Cmax ATB

Roberts JA, Crit Care Med 37 (3) 2009

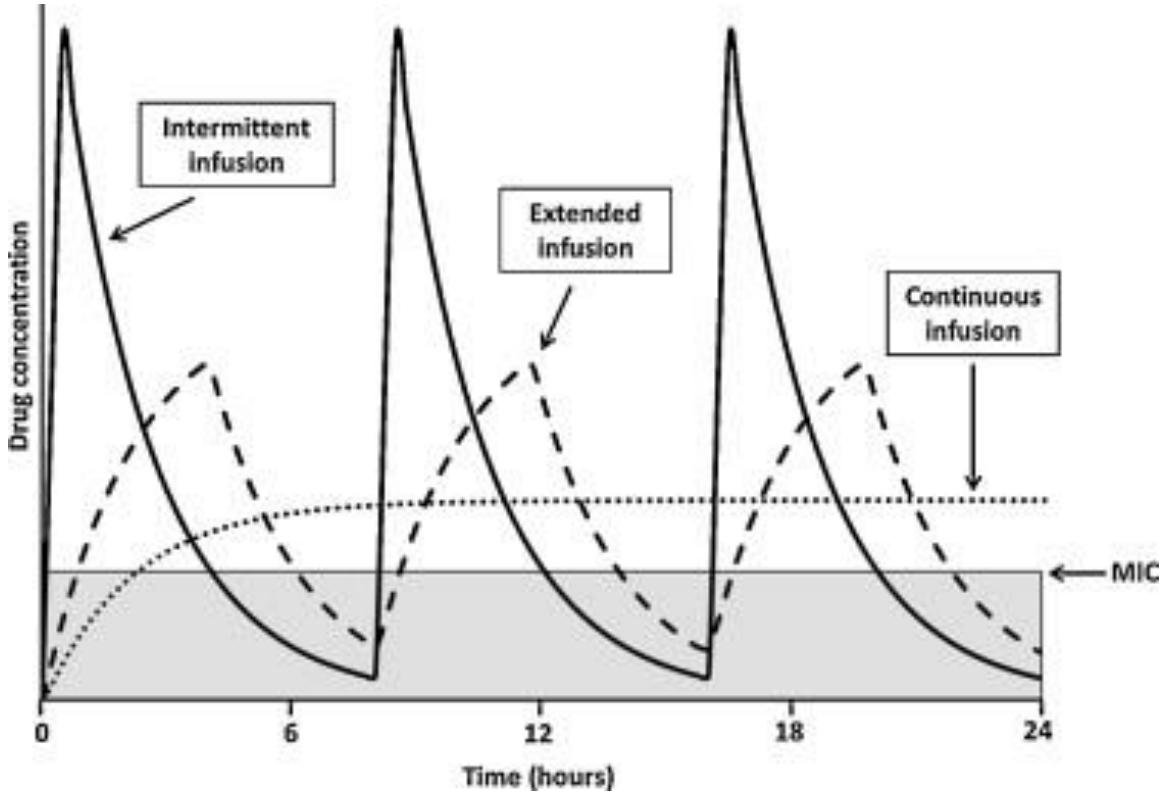
Time > MIC

β Lactams
Carbapenems
Lincosamids
Clindamycins
Vancomycine



$$\%Time > MIC \approx Ln\frac{Dose}{Vd \times MIC} \times \frac{T\,1/2}{Ln2} \times \frac{100}{\tau}$$

Way of administration
prolonged/continuous infusion



Time above the minimum inhibitory concentration (MIC) for intermittent, extended and continuous infusion of time-dependent drugs. Extended or continuous infusion of time-dependent drugs can improve the percentage of the dosing interval above the MIC...

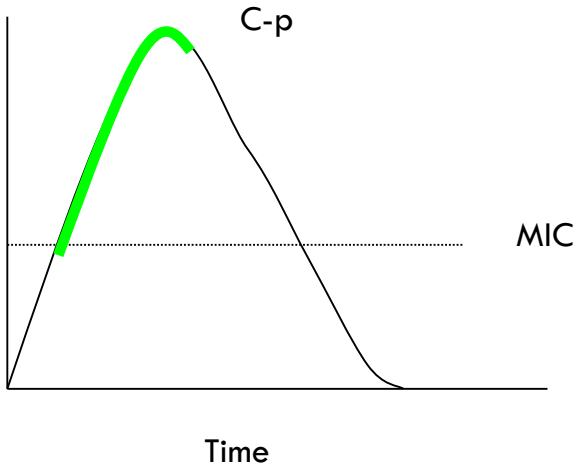
Downes KJ. International Journal of Antimicrobial Agents, Volume 43, Issue 3, 2014, 223 - 230

Time dependent killing activity and minimal persistent effects

- Maintain blood concentrations above MIC for prolonged time periods
- T>MIC ratio is the pK.pD predictor of efficacy of these antibacterials and to attain the best values of this parameter
- These drugs should be given by continuous infusion
- B- lactams
  - Constant controversy
  - Penicillin, monobactams, cephalosporins, carbapenems
  - No relation to the survival, continuous infusion vs extended infusion
  - Continous or extended infusion of β-lactam antibacterials leads to similar clinical results

Cmax / MIC

Aminoglycosides
Metronidazole



- **Bioavailability (%)**
- **clearance**
- **Rate of absorptione Rate of elimination**
- **Accumulation factor**

PK

$$\frac{C\,\max}{MIC_{90}}$$

PD

Concentration dependent killing activity and moderate to prolonged persistent effects

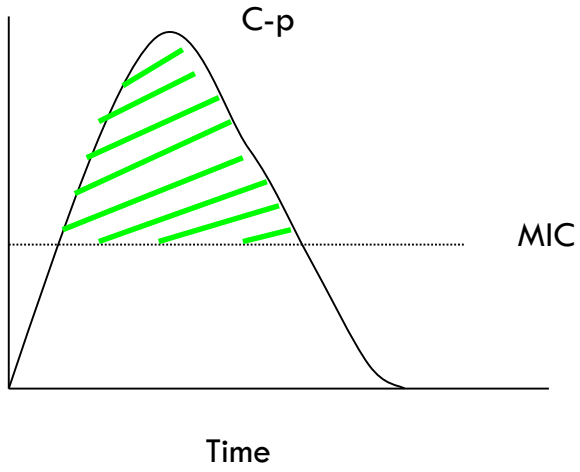
- More rapid killing effect against micro organisms than low concentrations
  - Allows the administrations of high doses with widely separated frequencies of administration

- Aminoglycosides
  - Doses of these antimicrobials administered to critically ill patients are frequently insufficient

Rea RS, et al. Suboptimal aminoglycoside dosing in critically ill patients. Ther Drug Monit 2008; 30: 674-81

AUC/MIC

Quinolones
Tetracyclines
Glykopeptidy
Linezolid



PK

$$\frac{AUC}{MIC} = \frac{Dose/Clearance}{MIC_{90}}$$

PD

Concentration dependent killing activity and moderate to prolonged persistent effects

- Fluoroquinolones
  - Cut off of 125 for the AUC/MIC ratio has been proposed
  - In critical ill patients, very complex given that pharmacokinetics of these and multiple variation related to changes in renal function and high inter-individual variability
  - Using a Monte Carlo dosing simulation, doses of 400mg every 8-12hrs givento 1-2 patients did not reach the necessary killing concentrations *for P.aeruginosa, A.baumannii strains*

Khachman D, et al. Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations. J Antimicrob Chemother 2011; 66: 1798-809

Time dependent killing activity and moderate to prolonged persistent effects

- Glycopeptides (Vancomycin, Teicoplanin)
  - Significant controversy in regarding the efficiency by which vancomycin kills GPB and the potential misuse of the drug
  - In humans, AUC/MIC value >350 was an independent factor associated with clinical success in patients with S.aureus proven lower respiratory tract infection
  - Difficulty in obtain multiple serum vancomycin concentration,

  → Cmin monitoring has been recommended as the most accurate and practical method
  - The duration of effect is longer and the possibility of regrowth of micro-organisms during the dosing interval is more limited

Time dependent killing activity and minimal persistent effects

- Linezolid
  - T>MIC and AUC/MIC are the pK/pD predictors of efficacy
  - With continuous infusion, AUC/MIC 80-120 more frequently than with intermittent infusion
  - According to pK/pD parameters, continuous infusion has theoretically advantages over intermittent infusion in this population

    Adembri C, et al. Linezolid pharmacokinetic/ pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. Int J Antimicrob Agents 2008; 31: 122-9

Table 1 Recommended and PK-adjusted regimens for aminoglycosides, broad-spectrum β-lactams and vancomycin. Dosages are proposed in case of normal renal function and to target less susceptible strains. Daily regimens of aminoglycosides will depend on the C_{max}/MIC ratio obtained with the previous administrations and on the C_{min}. Continuous infusion is applied when drug is administered over 24 h. Extended infusion is scheduled as 3 to 4-hour administration for piperacillin and 3-hour administration for meropenem

	Recommended loading dose	Recommended daily dose	PK target	PK adjusted loading dose	PK adjusted daily dose
Amikacin	15 mg/kg	–	C_{max}/MIC > 8–10	25–30 mg/kg	–
Tobramycin	5–7 mg/kg	–	C_{max}/MIC > 8–10	8–9 mg/kg	–
Gentamycin	5–7 mg/kg	–	C_{max}/MIC > 8–10	8–9 mg/kg	–
Cefepime	2 g	2 g/8 h	70% T > 4 x MIC	2 g	6 g CI
Ceftazidime	2 g	2 g/8 h	70% T > 4 x MIC	2 g	6 g CI
Piperacillin	4 g	4 g/6 h	50% T > 4 x MIC	4 g	4 g q6h ED
Meropenem	1 g	1 g/8 h	40% T > 4 x MIC	1 g	1–2 g/8 h ED
Vancomycin	15 mg/kg	15 mg/kg/12 h	C_{min} > 15–20 μg/mL (II) C_{min} > 20–30 μg/mL (CI)	35 mg/kg in 4 h	30–40 mg/kg CI

CI continuous infusion; C_{max} peak concentration; *II* intermittent infusion; *MIC* minimal inhibitory concentration; *T>MIC* time above the MIC.

Comparision of hydrophilic and lipophilic ATB related with PK properties

	Hydrophilic ATB	Lipophilic ATB
General PK characteristics	• Low Vd • Predominant renal CL • Low intracellular penetration • Inactive against intracellular pathogens	• High Vd • Predominant hepatic SL (Drug-drug interactions) • Good intracellular penetration • Active against intracellular pathogens
Altered ICU PK	• Higher Vd • Higher or lower CL dependent on renal function	• Vd largely unchanged • Higher or lower CL dependent on hepatic function
Examples	β-lactams Aminoglycosides Glycopeptides Linezolid Colistin	Fluoroquinolons Makcrolides Lincosamides Tigecykline

Influence of basic pharmacokinetic parameters

Drug clearance (CL)	Volume of distribution (Vd)
pathophysiology Function of elimination organs increase of cardiac output (increased flow, crystalloid / colloid NA-sepsis, burns)	**sepsis** leakage of fluid into the third compartment volume dependence hypoalbuminemia
Drug interactions induction inhibition binding to a proteins drug incompatibilites	**ascites**
Using RRT • selected method of elimination (Diffusion / convection) • technical adjustment methods (Qb, Qd, Qd predilutions / Postdilution) • physicochemical properties of ATB (Mw, lipophilicity, hydrophilicity, binding to proteins) • patient parameters (Residual filtration, nonrenal CL)	**obesity**

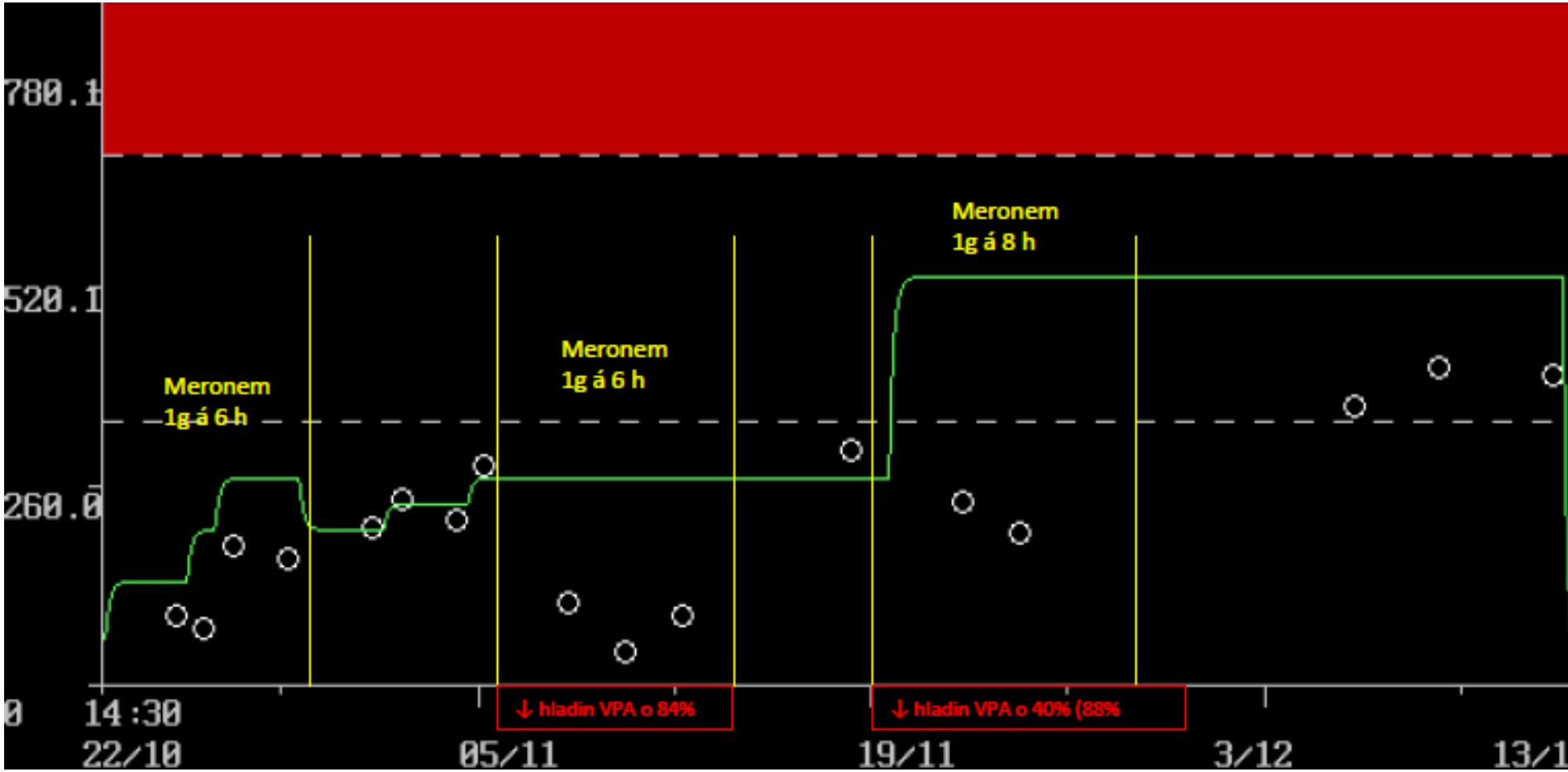
hydrophilic

lipophilic

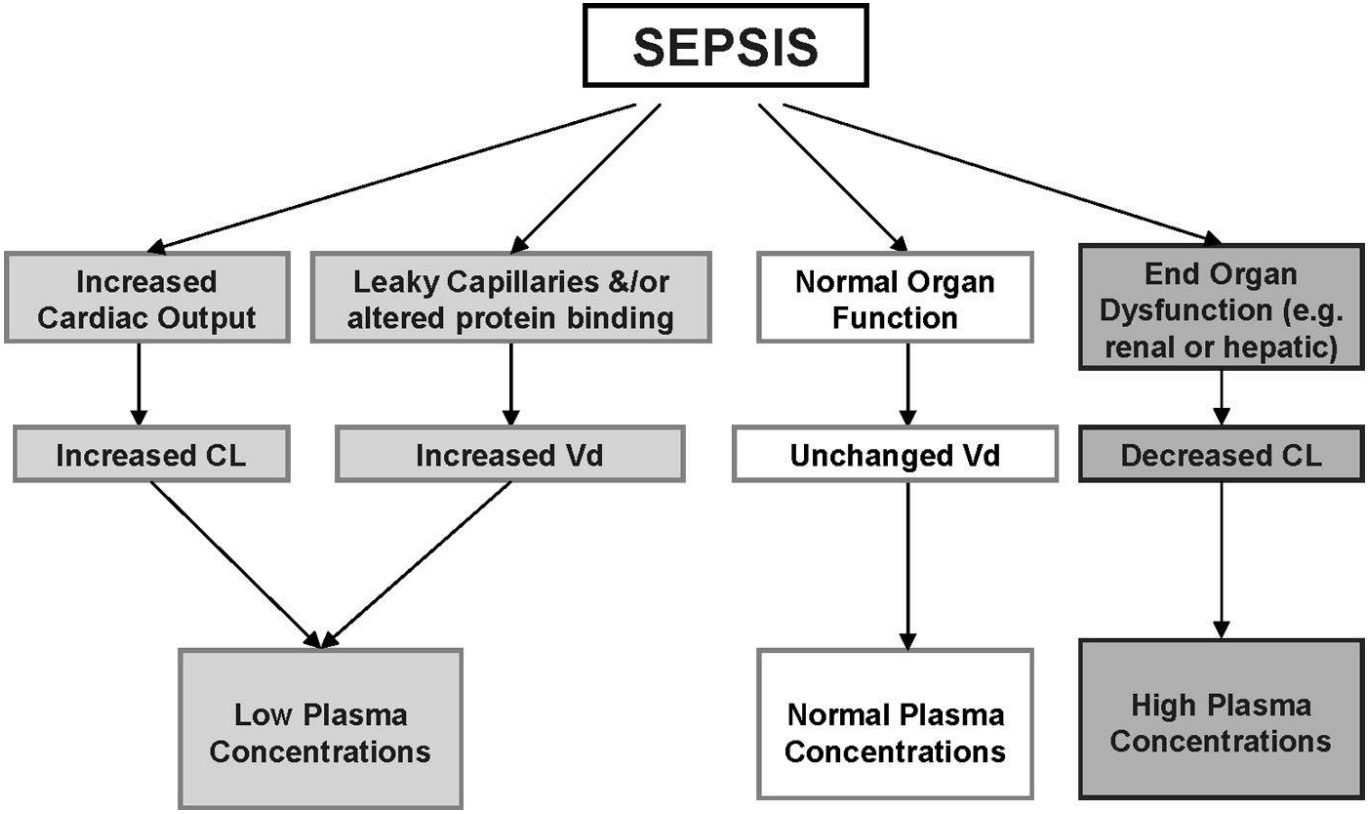
Case report

- Woman, 27 years, 58 kg, 165 cm
- laparoscopic appendectomy, 2nd day release at home, there colaps state, transported to ICU, massive pulmonary embolism
- CPR for cardiac arrest with the development posthypoxic status epilepticus – administered valproic acid (1600 mg/day), intubated
- Pneumoia treated with meropenem (1 g after 6 hours)
- Unadequate concentration of valproic acid althought the daily dose was increased on 6 000 mg

What is the management of this drug-drug interactions?



Schematic representation of the basic pathophysiological changes that can occur during sepsis and their subsequent pharmacokinetic effects.



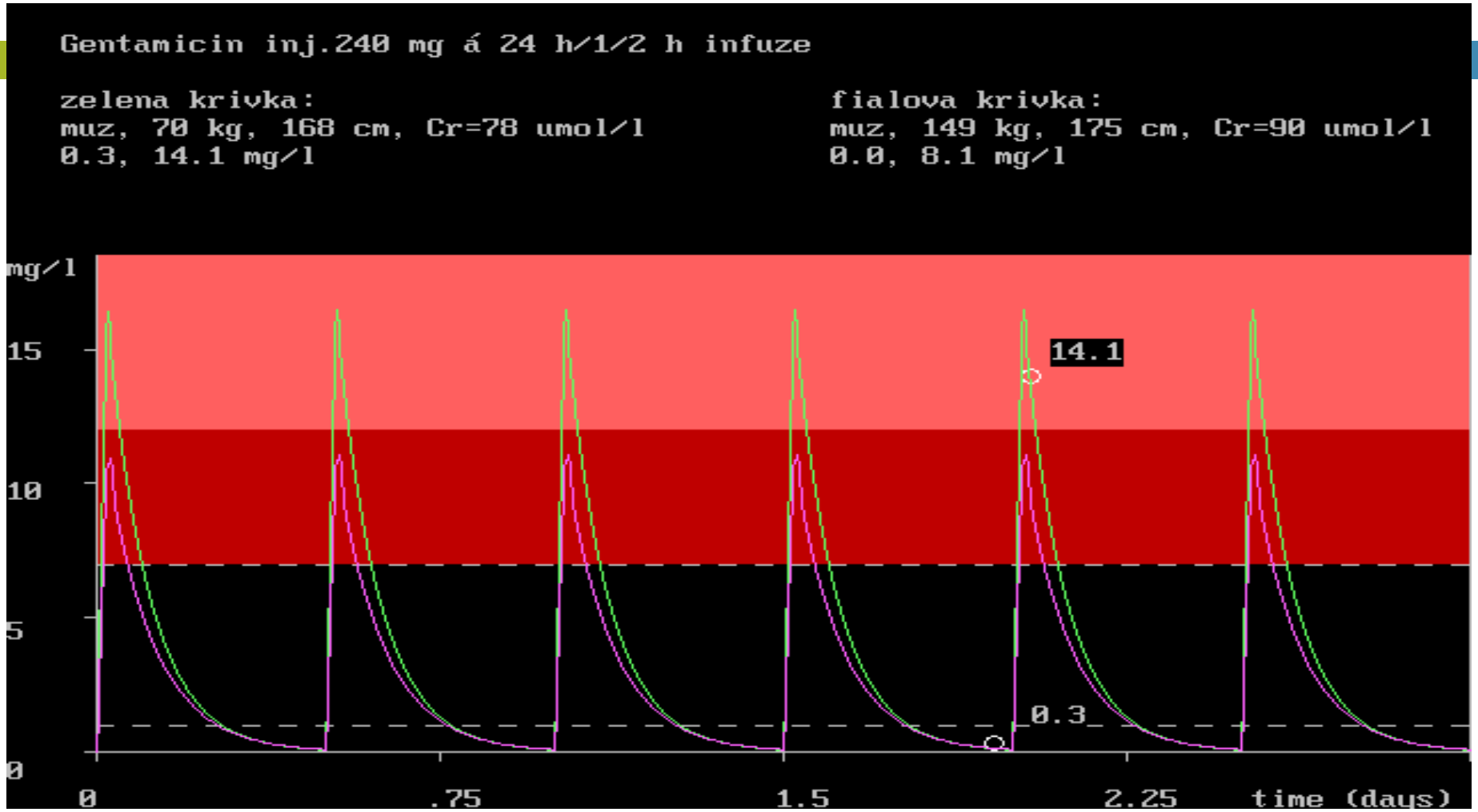
Roberts JA, Crit Care Med 37 (3) 2009

Guidelines therapeutic range of plasma concentration aminoglycosides

Table 1: Key Parameters for Aminoglycoside Antibiotics

Therapeutic Serum Concentrations		
Gentamicin, tobramycin	*Conventional dosing*[1] Peak 4-10 mcg/mL Trough < 2 mcg/mL	*Once-daily dosing*[5,6] Peak 20 mcg/mL Trough - undetectable
Amikacin	*Conventional dosing*[1] Peak 15-40 mcg/mL Trough <5- 10 mcg/mL	*Once-daily dosing* Peak 40- 60 mcg/mL Trough -undetectable
Volume of distribution[1]	0.25 L/kg (0.1-0.5 L/KG) 0.5 L/kg (children < 5 yrs)	-
Half-life[4]	~2-3 hr – normal renal function 30-60 hr – anephric patients	-

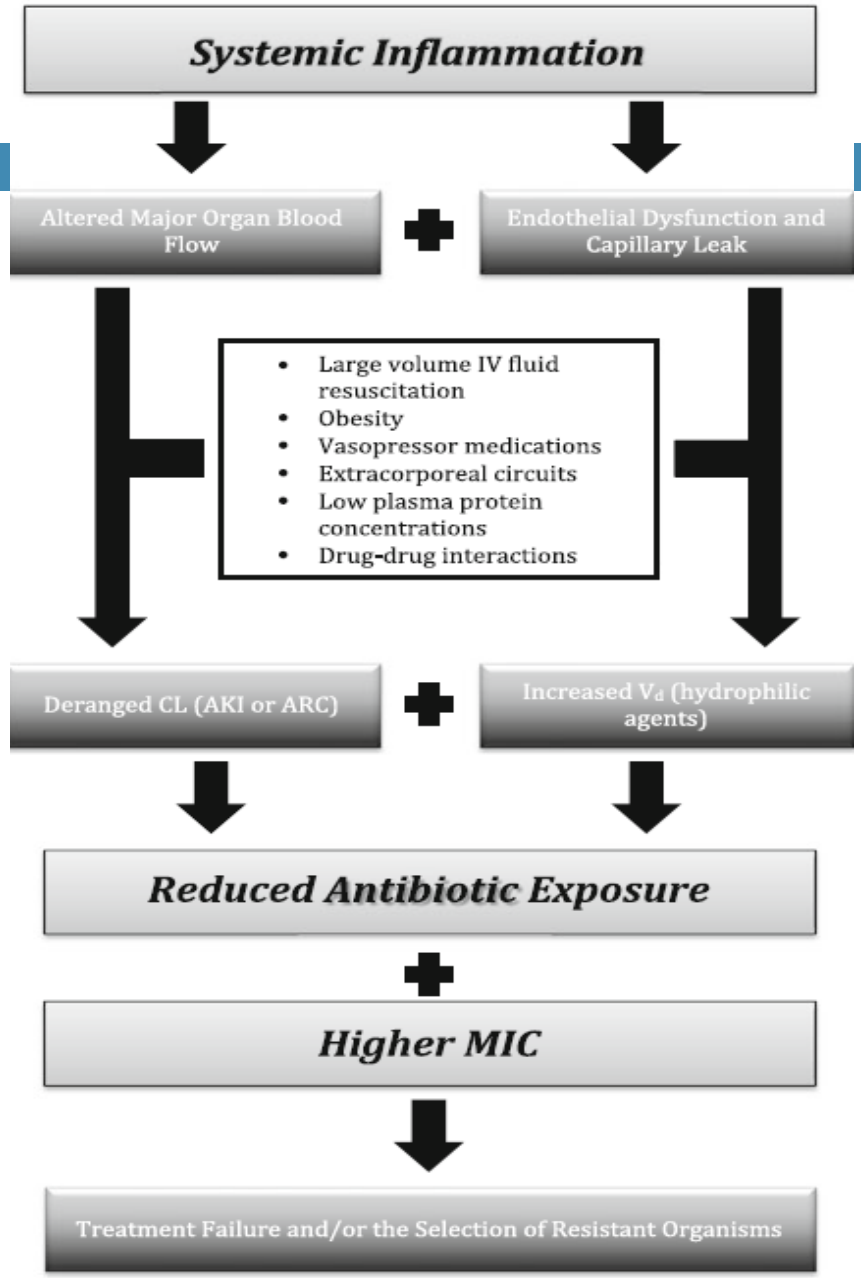
Shaw B.: Applied pharmacokinetics and pharmacodynamics, Lippincott Williams Wilkens, Philadelphia, 2006



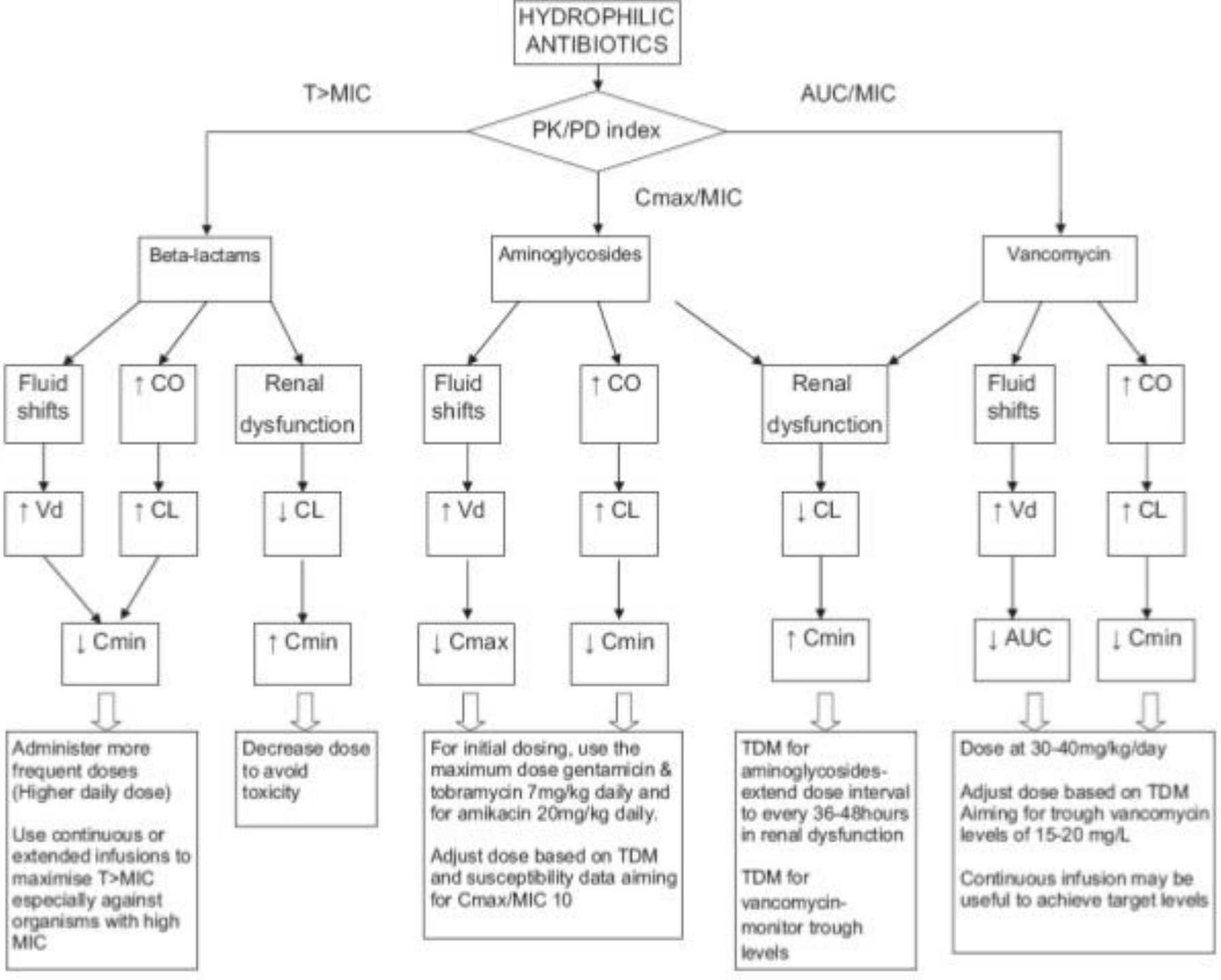
Considering the low Vd AMG has a small change of the extracellular fluid bulky fatty tissue the great importance for Vd changes.

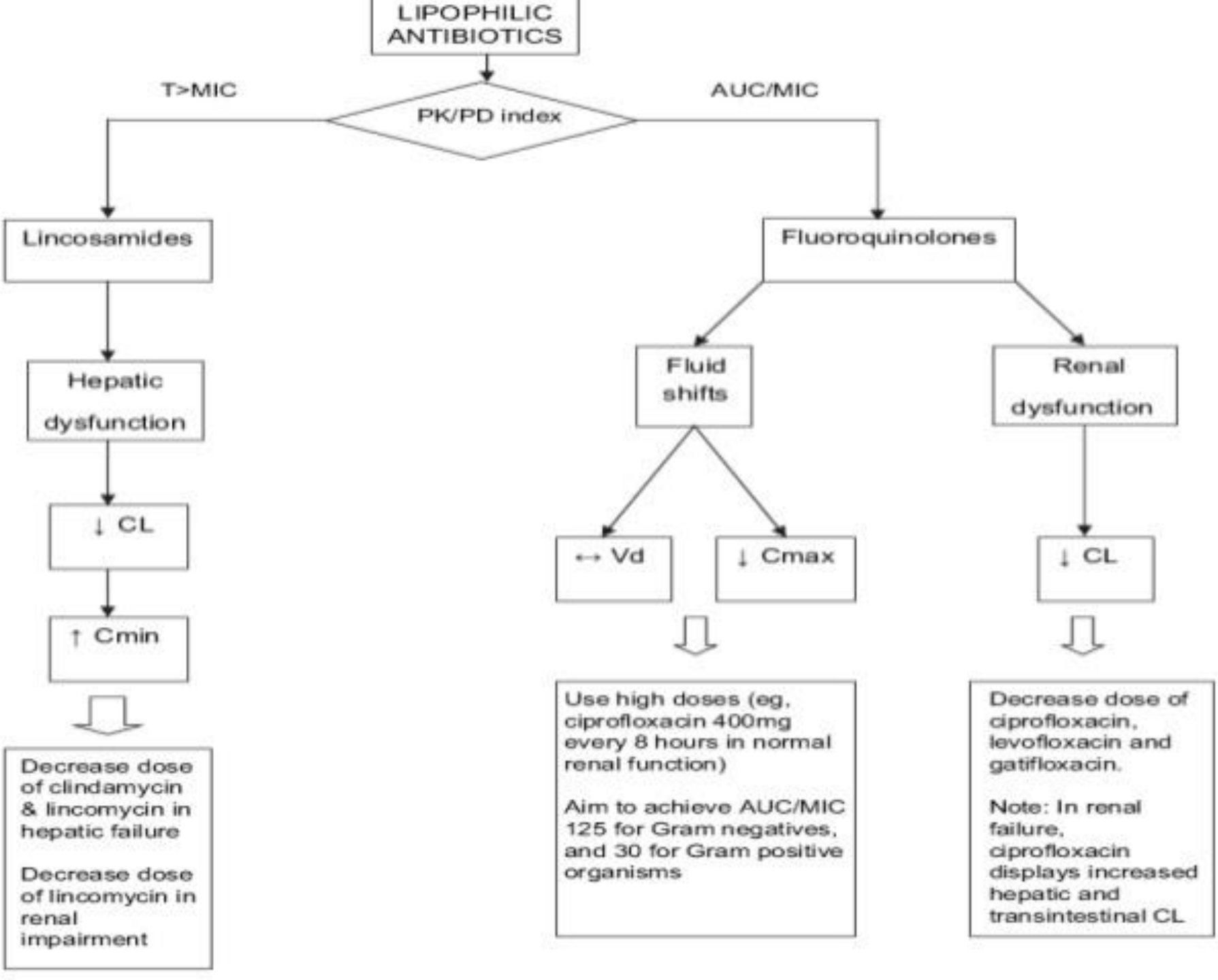
Altered physiology in the critically ill and the impact on antibiotic PK/PD.

ARC augmented renal clearance
AKI acute kidney injury,
CL clearance,
IV intravenous,
MIC minimum inhibitory concentration,
Vd volume of distribution



Udy, AA. Intensive Care Med (2013) 39:2070–2082

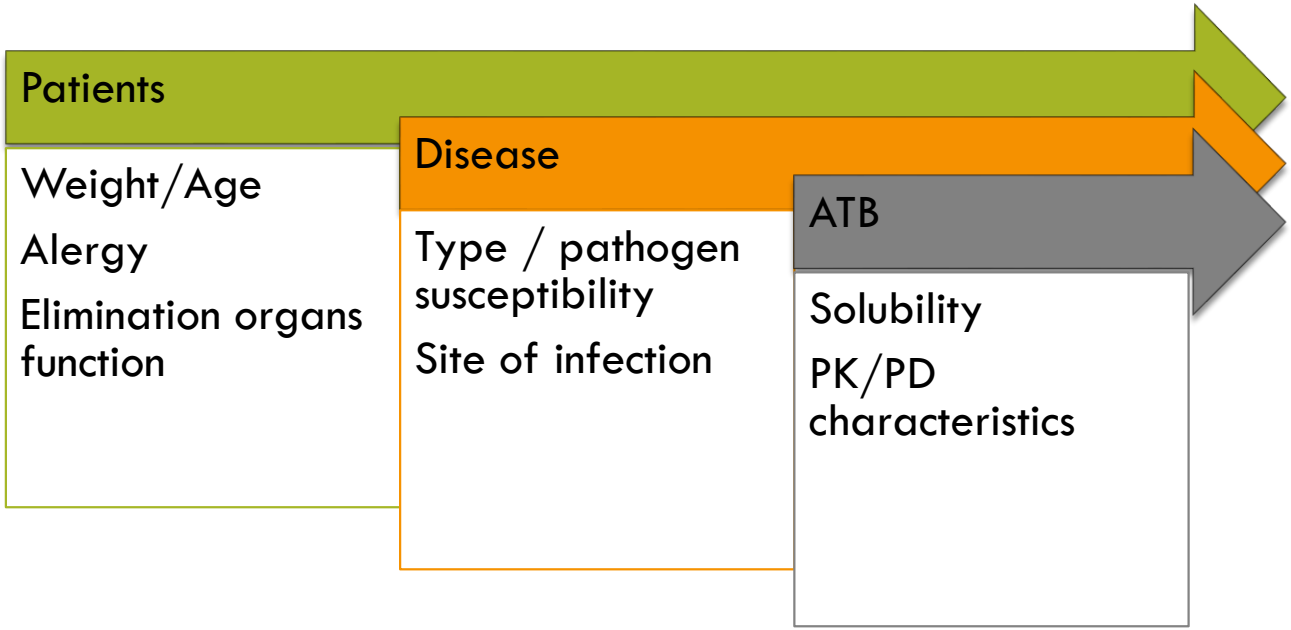

HYDROPHILIC ANTIBIOTICS
PK/PD index
T>MIC
Cmax/MIC
AUC/MIC
Beta-lactams
Aminoglycosides
Vancomycin
Fluid shifts
↑ CO
Renal dysfunction
Fluid shifts
↑ CO
Renal dysfunction
Fluid shifts
↑ CO
↑ Vd
↑ CL
↓ CL
↑ Vd
↑ CL
↓ CL
↑ Vd
↑ CL
↓ Cmin
↑ Cmin
↓ Cmax
↓ Cmin
↑ Cmin
↓ AUC
↓ Cmin
Administer more frequent doses (Higher daily dose)
Use continuous or extended infusions to maximise T>MIC especially against organisms with high MIC
Decrease dose to avoid toxicity
For initial dosing, use the maximum dose gentamicin & tobramycin 7mg/kg daily and for amikacin 20mg/kg daily.
Adjust dose based on TDM and susceptibility data aiming for Cmax/MIC 10
TDM for aminoglycosides- extend dose interval to every 36-48hours in renal dysfunction
TDM for vancomycin- monitor trough levels
Dose at 30-40mg/kg/day
Adjust dose based on TDM Aiming for trough vancomycin levels of 15-20 mg/L
Continuous infusion may be useful to achieve target levels


LIPOPHILIC ANTIBIOTICS
PK/PD index
T>MIC
AUC/MIC
Lincosamides
Hepatic dysfunction
↓ CL
↑ Cmin
Decrease dose of clindamycin & lincomycin in hepatic failure
Decrease dose of lincomycin in renal impairment
Fluoroquinolones
Fluid shifts
Renal dysfunction
↔ Vd
↓ Cmax
↓ CL
Use high doses (eg, ciprofloxacin 400mg every 8 hours in normal renal function)
Aim to achieve AUC/MIC 125 for Gram negatives, and 30 for Gram positive organisms
Decrease dose of ciprofloxacin, levofloxacin and gatifloxacin.
Note: In renal failure, ciprofloxacin displays increased hepatic and transintestinal CL

Optimalization of ATB therapy

- Selection of appropriate ATB
- Early initialization of ATB therapy
- Choosing the correct loading and maintenance dose
- The way of administration – prolonged/continual infusion

Depending on factors:



Guidelines therapeutic range of plasma concentration of vancomycine

Table 1: Vancomycin half-life [1].

Age group	Half-life
Neonates	6–10 hours
3 months to 4 years old	4 hours
>4 years old	2.2–3 hours
Adolescents	Not well defined (hypothesized to be similar to an infant)
Adults	5–8 hours

Table 2: Vancomycin dosing regimens [1, 2].

Age group	Dosing Regimen
Neonates	10–15 mg/kg every 6–18 hours depending on PMA and PNA
Infants, children, and adolescents	10 mg/kg every 6 hours (traditional dosing) or 15–20 mg/kg every 6–8 hours (serious infection)
Adults	15–20 mg/kg every 8–12 hours
Moses H. Cone Hospital (pediatrics)	15 mg/kg every 8 hours

PMA: postmenstrual age; PNA: postnatal age.

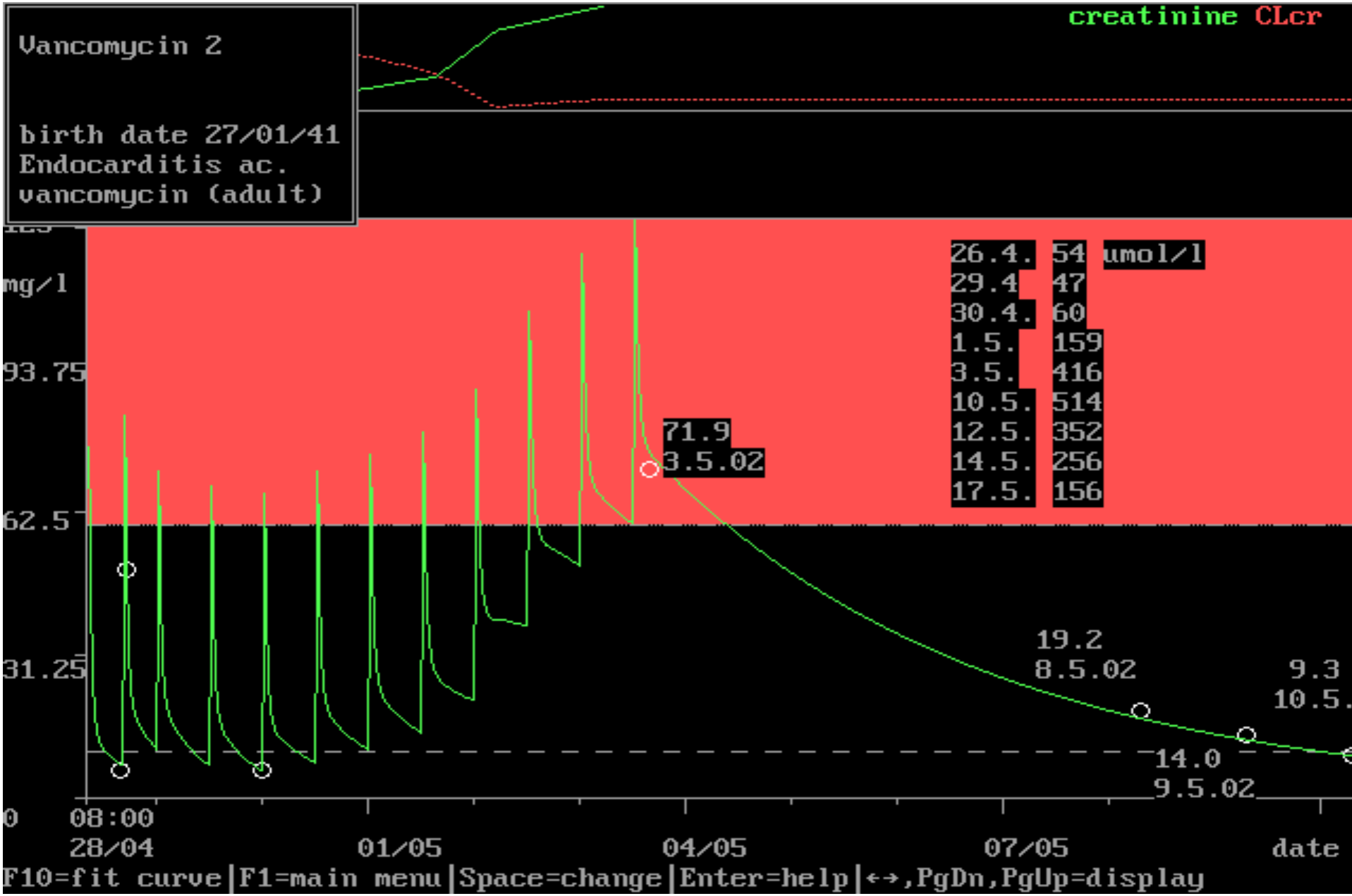
Guidelines therapeutic range of plasma concentration vancomycine

Optimal trough concentration (see also Optimal trough concentration—complicated infections)	Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid development of resistance. For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC:MIC of 400.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Optimal trough concentration—complicated infections (bacteremia, endocarditis, osteo-myelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*)	Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations

http://www.ashp.org/doclibrary/bestpractices/tpsvanco.aspx

Case report

- Man, 62 years, 75 kg, 175 cm
- Sepsis, septic shock
- initial therapy, a huge volume dependence,
- Vancomycin i.v. 1500 mg bid 12 h/1h inf. , sCr=54 umol/l.
  - plasma concentration (39.8 mg/l).
- Recommendations: to continue in dose regiment for four days and then to perform sample control before the next dose
  - plasma concentration (7 mg/l).
- Then comes the worsening of renal function, creatinine is gradually increasing.
- The sample control was performed on 8. day and 7.5 hours after administration was found creatinemia 416 umol/l.
  - Plasma concentration (71.9 mg/l).
- Vancomycine was stoped and drop to a safe concentration lasted 7 days.

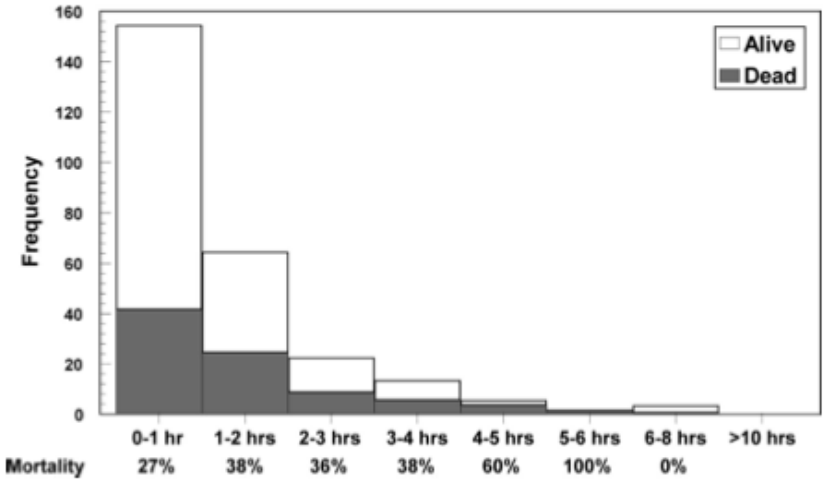


The drug accumulation in the body during therapy required monitoring levels throughout the treatment period!

Early ATB therapy

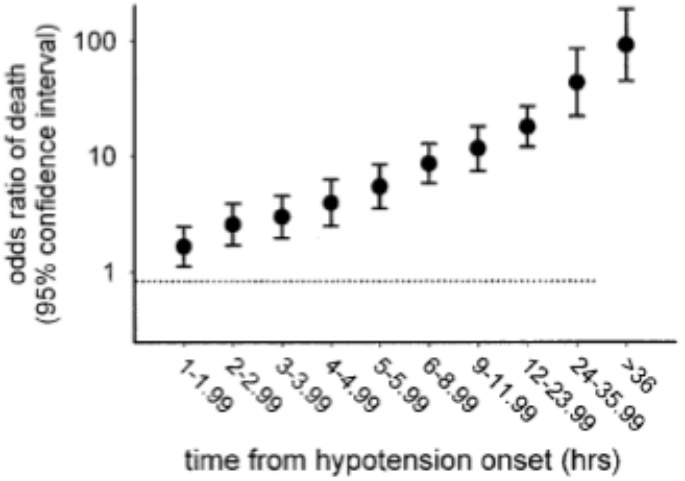
- Many large, observational studies have demonstrated that early initiation of antibiotic therapy is very closely related to improved survival
- Non-randomized-controlled data

Time from EDGT qualification to ABX



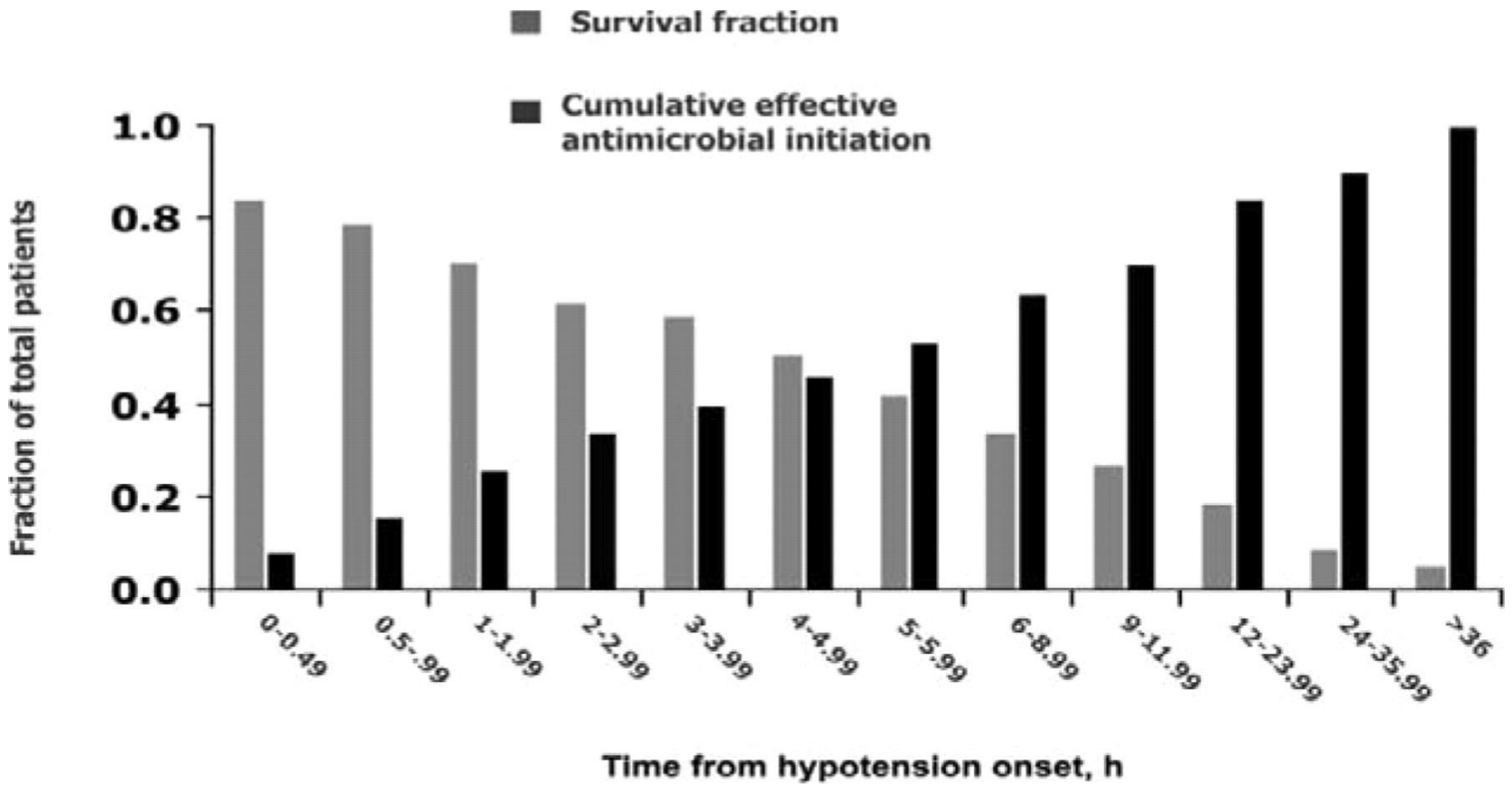
Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*. Critical Care Medicine 2010;38(4):1045–53.

Time from hypotension to appropriate ABX



Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Critical Care Medicine 2006;34(6):1589–96.

Early initiation of appropriate antibiotic therapy for septic shock and survival.



Deresinski S Clin Infect Dis. 2007;45:S177-S183

Clinical Infectious Diseases

Dose selection

Loading dose:

- The initial dose is typically used to ensure the achievement of therapeutic concentrations in the shortest possible time and to achieve bactericidal activity.
- This applies even in the antibiotics, which subsequently administered in several hours of infusion (carbapenems). After intravenous bolus antibiotic concentration decreases very rapidly particularly for distribution of the drug. If Vd is higher than assumed, the standard dose of antibiotics is inadequate and should be increased.

Recommendation:

- Physicians should choose a higher initial dose with aminoglycosides, β-lactams, glycopeptides and colistin in critically ill patients with sepsis.
- Subsequent doses should be adjusted according to the function of elimination organs.

(Moore RD, 1987, Taccone FS, 2010)

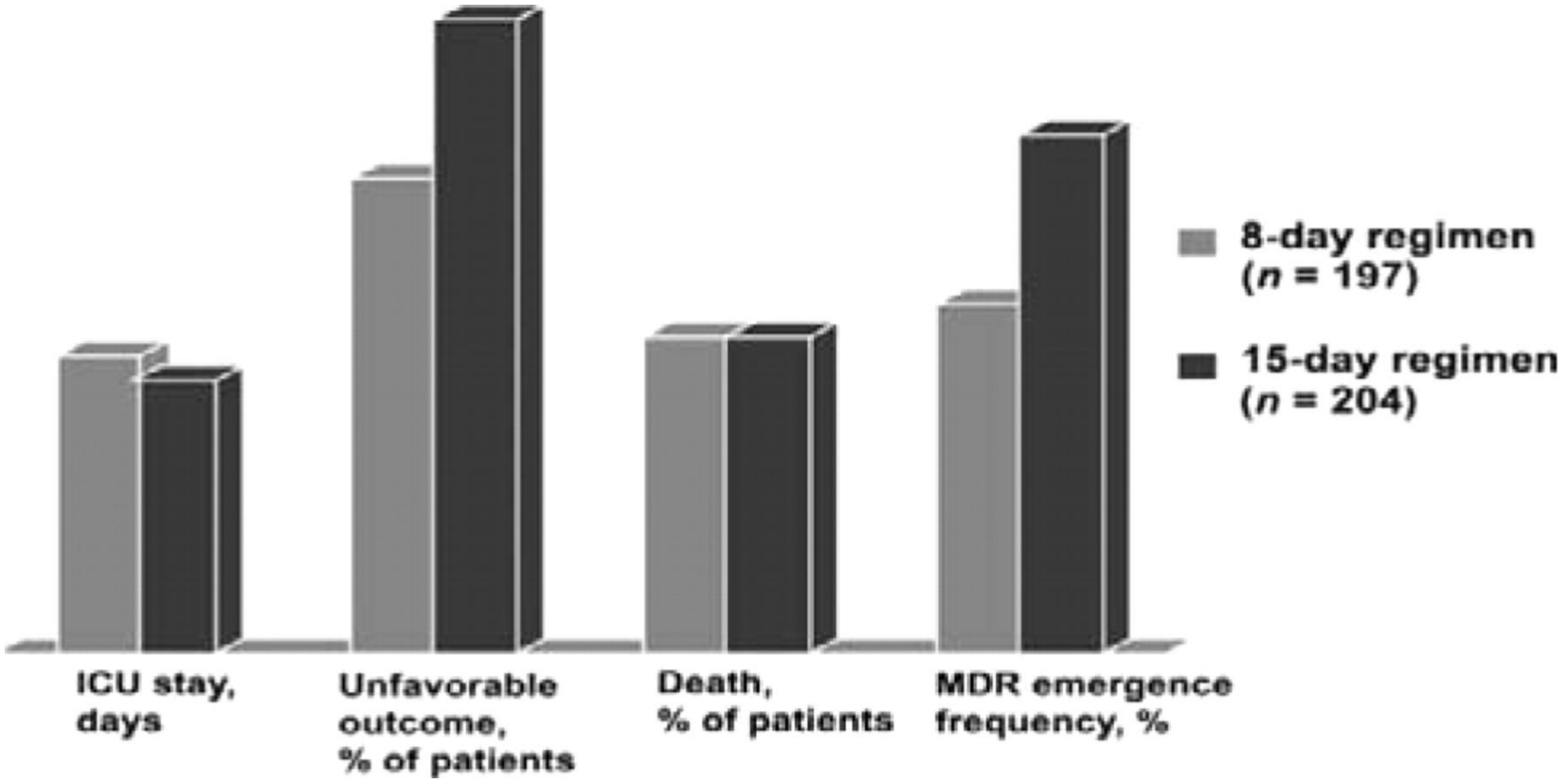
Dose adjustments at AKI

- Generally, in AKI the dose of ATB during the first 48 to 72 hours is not necessary to reduce. In risk ATB is necessary to adjust the dose according to the monitoring levels. (Blot, 2014).
- Generally, it is recommended to reduce the initial dose ATB in patients during CVVH (Pea F, 2007 Bouman SC, 2008).
- All these data show a significant correlation between disease severity and pharmacokinetics of antibiotics, which is not normally taken into account in most current dosing regimens (Udy AA, 2013).
- **ATB dosage recommended on the SPC is not adequate for patients with sepsis.**

Duration of antibiotic therapy

- The optimal duration of antibiotic therapy for bacteremia is unknown. There appears to be some evidence that would suggest that there is no significant difference in mortality, clinical and microbiological cure between shorter durations i.e. 5 – 7 days versus 8 -21 days in critically ill patients with bacteremia.

Appropriate empirical antibiotic therapy of ventilator-associated pneumonia: 8 vs. 15 days.



Deresinski S Clin Infect Dis. 2007;45:S177-S183

Strategies to optimize the use of antimicrobials in the ICU

- 1) De-escalation therapy
- 2) Antibacterial cycling
- 3) Pre-emptive therapy
- 4) Use of pharmacokinetic/pharmacodynamic parameters for dose adjustment

De-escalation therapy

- Initial administration of broad spectrum empirical treatment
  - To cover pathogens, most frequently related to the infection
- Rapid adjustment of antibacterial treatment once the causative pathogen has been identified
- Objective
  - Lower morbidity and mortality by an early achievement of an appropriate empirical treatment
  - Limit the appearance of bacterial resistance by a reduced antibacterial pressure
- Condition that needed-strategy
  - Epidemiolgical map of the bacterial ecosystem including susceptibility pattern of the most frequent pathogen
  - Rapid response of microbiological studies
  - Compliance with the recommendation of adjusting initial empirical treatment to definite microbiological diagnosis

De-escalation therapy

- Applicability of this strategy, failed
  - Absence of microbiological results
  - Isolation of multi-resistant pathogens preventing de-escalation
  - Reluctance of some clinicians to change antibacterials in patients with a favorable clinical course despite persistence of severity of illness

- Despite limitations, antibacterial de-escalation therapy has been recommended
  - ATS guideline for the management of adults with hospital acquired, ventilator associated, and healthcare associated pneumonia, AJRCCM 2005;171:388-416

Antibacterial cycling

- The scheduled rotation of one class of antibacterials
  - One or more different classes with comparable spectra of activity
  - Different mechanisms of resistance
- Some weeks and a few months
- Objective
  - Reduce the appearance of resistances by replacing the antibacterial before they occur and preserving its activity to be re-introduced in the hospital in a later cycle

Pre-emptive therapy

- The administration of antimicrobials in certain patients at very high risk of opportunistic infections before the onset of clinical signs of infection
  - Developed in hematological patients and/or transplant recipients based on the use of serological tests that advanced the diagnosis of some infections
  - CMV, aspergillosis
  - In critical illness patients to patients at high risk of candidemia or invasive candidiasis

    : In the absence of serological test to establish an early diagnosis of invasive candidiasis, different scores based on clinical and/or microbiological data

A bedside scoring system (Candida score) for preemptive antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med 2006; 34: 730-7

- In a large cohort of nonneutropenic critically ill patients in whom Candida colonization was prospectively assessed, a "Candida score" >2.5 accurately selected patients who would benefit from early antifungal treatment.

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

ICU, intensive care unit.

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

How to optimize antibiotic administration in critically ill patient

- 1) β-lactams
  - Active against most organisms recovered form ICU patients
  - Drug levels are insufficient in patients with severe infections
  - Cefepime (2g taken every 12hr) concentrations were more than 70% above target concetnrations in less than half of patients with sepsis

Ambrose PG, Owens Jr RC, Garvey MJ, et al. Pharmacodynamic considerations in the treatment of moderate to severe pseudomonal infections with cefepime. J Antimicrob Chemother. 2002;49:445–5

→ Cefepime (2g every 8hr), recently

  - Serum cefepime and ceftazidime levels below therapeutic levels after a few hours in most cases in septic patients with normal renal function

Lipman J, Gomersall CD, Gin T, et al. Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother. 1999;43:309–11.

How to optimize antibiotic administration in critically ill patient

- 1) β-lactams
  - Piperacillin concentration, above therapeutic levels for most of the time interval in patients with sepsis
  - Administration of piperacillin by continuous infusion, with a loading dose, achieved superior pharmacodynamic targets compared with conventional bolus dosing in septic patients

Roberts JA, et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. Int J Antimicrob Agents 2010, 35:156–163.

  - Meropenem concentration, adequate in most of the studies in critically ill patients
  - But in severe infection,mostly after cardiac surgery, meropenem had adequate serum concentration for at least 50% of the time in patients with normal and impaired renal function

Kitzes-Cohen R, Farin D, Piva G, et al. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. Int J Antimicrob Agents. 2002;19:105–10.

How to optimize antibiotic administration in critically ill patient

- Monitoring of several antibiotics in a large cohort of ICU septic patients, showing that dose adjustments are necessary to optimize drug concentrations in most of them

- Early phase of sepsis, broad-spectrum β-lactams should be administered more frequently or in doses larger than suggested in non septic patients with a dramatic increased of therapy costs

- Continous infusion or extended β-lactam infusion are required to optimize pathogen exposure to bactericidal concentrations of these drugs
  - Roberts JA, Lipman J: Pharmacokinetic issues for antibiotics in The critically ill patients. Crit Care Med 2009, 37:840–851

How to optimize antibiotic administration in critically ill patient

- 2) Vancomycin
  - Higher than recommended doses of vancomycin were necessary to optimize drug concentrations and rescue patients from septic shock d/t GPB
  - Administration of the conventional dose of vancomycin (15mg/kg of BW every 12hr) would probably fail to achieve therapeutic drug concentraions in the majority of critically ill patients

→ Continuous infusion with 30mg/kg daily dosage has been proposed to optimize PD vancomycin

Pea F, Viale P. Should the currently recommended twice-daily dosing still be considered the most appropriate regimen for treating MRSA ventilator-associated pneumonia with vancomycin? Clin Pharmacokinet. 2008;47:147–52.

- Continuous infusion, faster time to achieve target drug concentrations, lower daily dose, reduced therapy costs than intermittent dose

Wysocki M, et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother. 2001;45:2460–7.

How to optimize antibiotic administration in critically ill patient

- Clinical superiority of continuous infusion of vancomycin in a subgroup of patients with VAP d/t MRSA

  Rello J, Sole-Violan J, Sa-Borges M, et al. Pneumonia caused by methicillin-resistant Staphylococcus aureus treated with glycopeptides. Crit Care Med. 2005;33:1983–7.

- Continuous infusion with a 30mg/kg daily dosage has been proposed to optimize PD vancomycin

  Pea F, Viale P. Should the currently recommended twice-daily dosing still be considered the most appropriate regimen for treating MRSA ventilator-associated pneumonia with vancomycin? Clin Pharmacokinet. 2008;47:147–52.

- Slower onset of nephrotoxicity

  Ingram PR, Lye DC, Fisher DA, et al. Nephrotoxicity of continuous versus intermittent infusion of vancomycin in outpatient parenteral antimicrobial therapy. Int J Antimicrob Agents. 2009;34:570–4.

Summary

- Antibiotics are amongst the most commonly used therapies in critical care
- Optimising antibiotic use improves patient outcomes
- Optimising antibiotic use should minimise pressures on emerging antibiotic resistance

Summary

- **Early administration of adequate antibiotic at the right dose is crucial for the treatment of sepsis and positively influences the prognosis**
- **In critically ill patients are often required increased doses of antibiotics than other patients**
- **In acute organ failure the dose of antibiotics within the first 48-72 hours does not reduce**
- **For toxic ATB (aminoglycosides, vancomycin) adjust the dose according to plasma levels of antibiotics**
- **ATB administered according to their PK / PD properties**

Literature

- Gilbert DN.: The Sanford guide to antimicrobial therapy, Sperryville, USA, ISBN: 978-1-930808-60-70, 2013
- Aronoff, GR.: Drug Prescribing in Renal Failure, Dosing guidelines for adults and children, fifth edition,ACP, Philadelphia, USA, ISBN: 978-1-930513-76-1, 2007

  http://kdpnet.louisville.edu/renalbook/