

**EAHP congress Gothenburg, 2018**

**Seminar CPS3: Antimicrobial stewardship  
- growing a positive culture**



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Dr. Thern: Antibiotic Stewardship  
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Campus Lübeck  
Germany

# Conflict of interest disclosure

- Dr. Thern
  - Nothing to disclose

## Self-assessment questions

- According to the EU guideline, only clinicians and microbiologists are key members of an ABS team
- Prolonged infusions are advantageous for time-dependent antibiotics in the ICU setting
- Antibiotic consumption data should be reported as densities

# University hospital Schleswig Holstein

- 2 campuses (Kiel, Lübeck)
- total: ca. 2200 beds
- ABS teams established since 2011

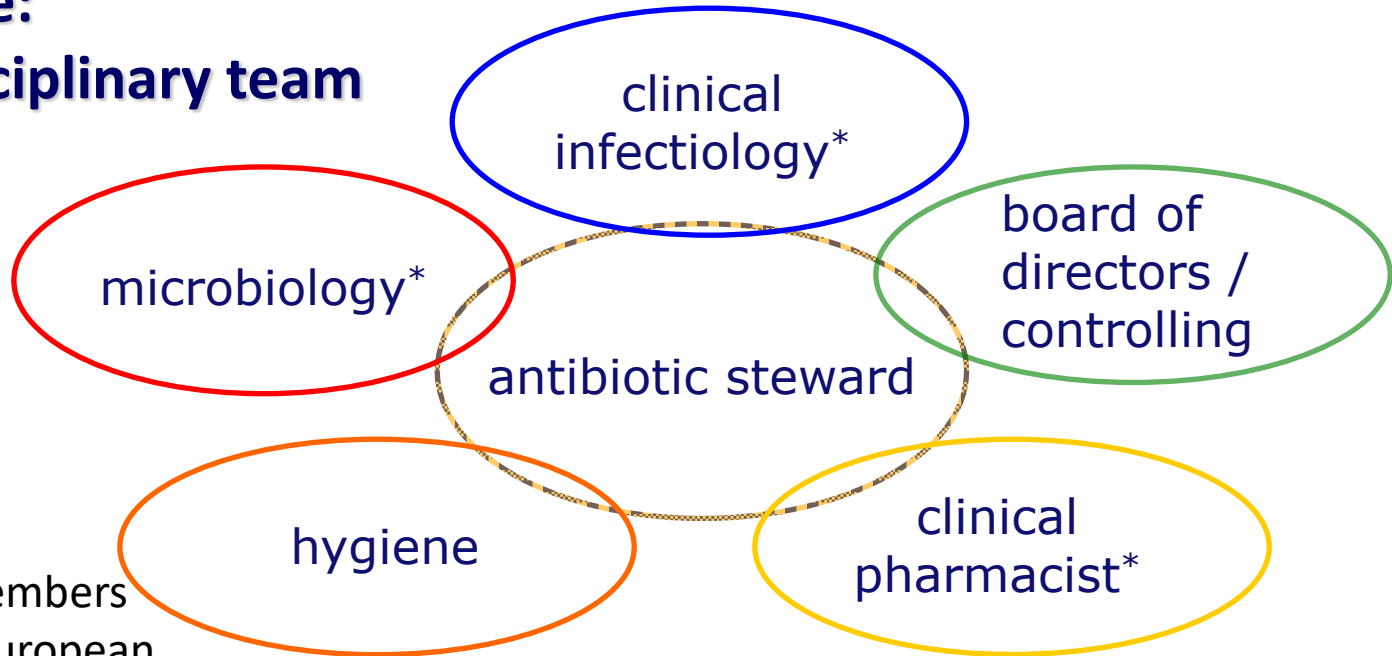




## – what about your hospital?

- ABS team
  - available / existent?
  - planned?
- Are **you** a member of the ABS team?

## Structure: multidisciplinary team



\* Key team members  
according to European  
guideline



# European Centre for Disease Prevention and Control

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**Antimicrobial stewardship**

[Carbapenem-resistant Enterobacteriaceae \(CRE\)](#)

[Clostridium difficile](#)

[Hand hygiene](#)

[Infections during endoscopic procedures](#)

[Methicillin-resistant Staphylococcus aureus \(MRSA\)](#)

[Organisation of infection prevention and control](#)

[Peri-operative antimicrobial prophylaxis](#)

[Projects: Antimicrobial resistance and healthcare-associated infections](#)

## Antimicrobial stewardship



### EUROPE

#### EUROPEAN COMMISSION

- [Commission Notice - EU Guidelines for the prudent use of antimicrobials in human health \(2017/C 212/01\) \(European Commission, 2017\)](#)

### AGENCIES

#### US CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) / EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (ECDC)

- [Structure and process indicators for hospital antimicrobial stewardship programs \(Transatlantic Task Force on Antimicrobial Resistance, 2015\) Summary the modified Delphi process for common structure and process indicators for hospital antimicrobial stewardship programs](#)

#### US CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

accessed: Feb 11, 2018

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Contents

## II *Information*

INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

### **European Commission**

2017/C 212/01

Commission notice — EU Guidelines for the prudent use of antimicrobials in human health ..... 1





antibiotic stewardship

## team – according to EU guideline

- Including ideally (in hospitals)
  - Clinician (if possible infectious disease specialist)
  - Hospital pharmacist
  - Microbiologist (if possible clinical microbiologist)

“The composition is dictated by the hospital size and level of care and by national and local provisions.”

“In hospitals, the elements of antimicrobial stewardship programmes should include... salary support and dedicated time for antimicrobial stewardship activities”

## 4.6. Pharmacists

Pharmacists in community and hospital settings have expertise in medicines and are the gatekeepers to the use of antimicrobials. As such, pharmacists can act as an important source of advice and information for patients and prescribers on the safe, rational and effective use of antimicrobials (including on side effects, adherence, adverse drug reactions, cautions & contraindications, interactions, storage & disposal and rationale for treatment). To this end, they need to be provided with appropriate training, guidelines and information in order to be able to encourage prudence in the prescribing of antimicrobials and manage patient expectations. In the hospital setting, a pharmacist should be a member of the antimicrobial stewardship team and actively involved in antimicrobial management in the multidisciplinary care team. The role of the pharmacist includes assessing the prescription in accordance with local policies for antimicrobial use; reviewing the antimicrobial duration; counselling on the use of restricted antimicrobials; giving advice on dosage, preparation and administration (especially for special patient cohorts such as children); and advising patients on the proper use of antimicrobials. Pharmacists should also be involved in monitoring antimicrobial use.



## Role of the pharmacist

- Focus on drug-related problems
  - ➔ appropriate dosing:
    - dose
    - mode of administration (e.g. route, duration of infusion)
    - frequency

## When prescribing an antimicrobial, prescribers should:

- ▶ Select an antimicrobial in accordance with relevant guidelines, at an appropriate dose, for the shortest effective duration and with appropriate route of administration (preferably oral if possible).
- ▶ Consider relevant host factors: age, comorbidities (e.g. immunodeficiency), renal and hepatic function, pregnancy, breastfeeding, allergies, presence of prosthetic material, potential drug interactions, body mass index and risk factors for antimicrobial resistance (e.g. history of recent antimicrobial use, history of recent travel).
- ▶ Promote allergy testing for patients with a history of allergic reaction to beta-lactams, as a measure to promote use of first-line antimicrobials in non-allergic patients.

Counselling by pharmacist may be helpful

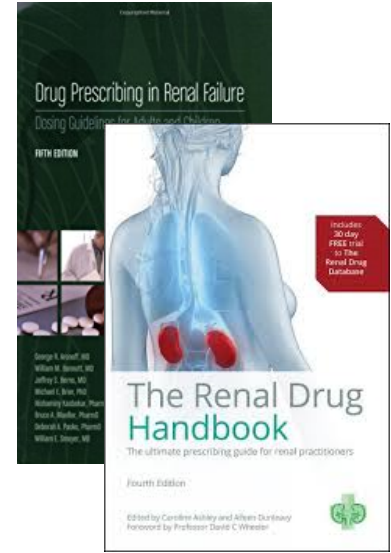


# Role of the pharmacist

## ➤ Renal dosing

- Literature search, e.g. in
  - ▶ tertiary literature, examples ⇒
  - ▶ primary literature (e.g. dosing for specific dialysis mode)
- Recommendation of a dose

patient-specific	micro-intervention
consensus for degree of renal insufficiency / dialysis mode	macro-intervention



edited by Ashley C, Dunleavy A.

# Role of the pharmacist

## ➤ obesity dosing

- Recommendation of a dose
  - “One size fits all”: Not for all antibiotics
  - No uniform approach, dosing may be based on
    - Standard dosing
    - Total body weight (e.g. for daptomycin)
    - Adjusted body weight (e.g. for aminoglycosides, but conflicting data)
    - Ideal body weight (e.g. for CMS)

# Therapeutic drug monitoring

- To confirm / optimize dosing strategies
  - especially for challenging scenarios
- common in ICUs:  
TDM of vancomycin, aminoglycoside trough concentrations

Tabah A, et al. ADMIN-ICU survey.  
J Antimicrob Chemother 2015; 70: 2671-7

# Tools for TDM

e.g. calculators by clincal.com

## Vancomycin Calculator

Advanced vancomycin pharmacokinetics tool

 [ClinCalc.com](http://clincalc.com) » [Infectious Disease](#) » Vancomycin Calculator


### Patient Parameters


Body weight:

Volume of distribution (Vd):

 L/kg

Therapeutic goal: 

Recommend loading dose: 

### Elimination Constant (Kel)

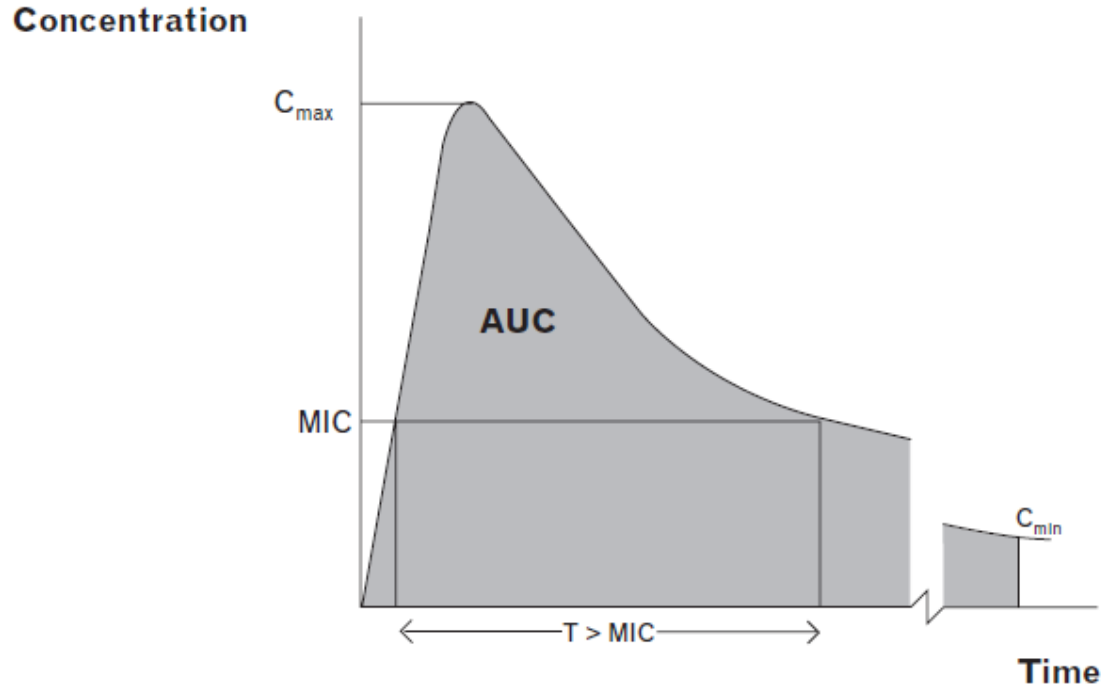
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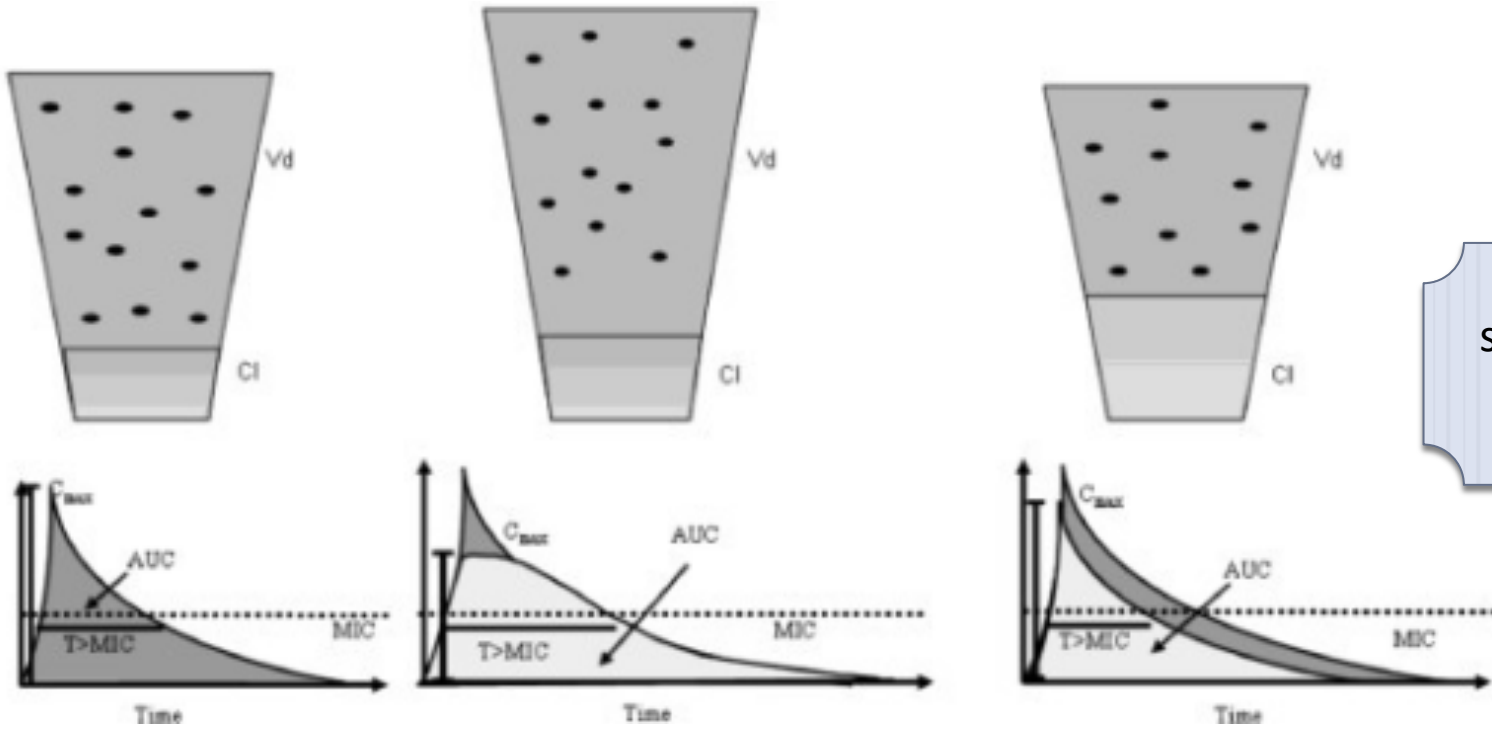
<http://clincalc.com/vancomycin/>



# Pharmacologic indices for antibiotic therapy



# pharmacokinetic changes of antibiotics in ICU patients



Wide spectrum of other scenarios

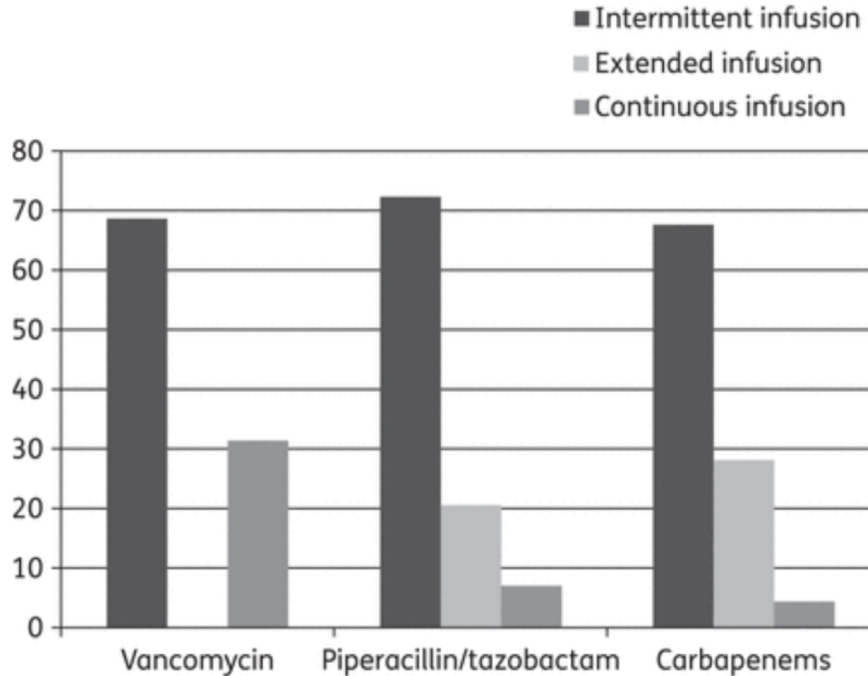
Healthy volunteer

increased Vd

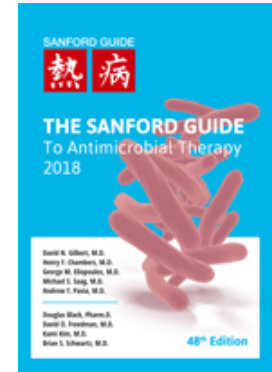
Increased clearance

# Prolonged infusions

Survey of infusion strategies (ICU patients)



Tabah A, et al. ADMIN-ICU survey.  
J Antimicrob Chemother 2011; 70: 2671-7



details e.g. in  
Sanford  
guide to  
antimicrobial  
therapy

## Role of the pharmacist

- Focus on
  - ➔ incompatibilities
    - may be influenced by
      - concentration of drugs
      - mode of administration (e.g. Y-site, admixture)

## Example:

**Case Report.** A 37-year-old woman who was scheduled for diagnostic laparoscopy received a single dose of cefuroxime intravenously as routine prophylactic antibiotic therapy after induction of general anesthesia. At this time the patient additionally received, through the same intravenous line, piritramide 7.5 mg/mL for postoperative pain management since the surgical procedure was almost completed. Piritramide immediately precipitated as white “snow.” Fortunately, the precipitate could be completely aspirated so that there was no risk of serious complications for the patient.

	Piritramide (mg/mL)					
	5	3.75	3	1.875	1	0.5
Precipitation with cefazolin (20mg/mL)	Yes	Yes	Yes	No	No	No

1:1 admixture in a syringe

Eckle VS, Grasshoff C. Anästhesist 2013; 62: 898-901

## Example cont.:

**Table 1.** Results of Precipitation Between Opioids and Cephalosporins

Cephalosporin	Precipitation				
	Sufentanil Citrate 5 µg/mL	Piritramide 7.5 mg/mL	Piritramide 0.5 mg/mL <sup>a</sup>	Alfentanil Hydrochloride 0.5 mg/mL	Fentanyl Citrate 0.05 mg/mL
Cefuroxime 30 mg/mL	No	Yes	No	No	No
Cefazolin 20 mg/mL	No	Yes	Not tested	No	No

<sup>a</sup>A 15 times lower concentration of piritramide was made by diluting pure piritramide 7.5 mg/mL in distilled water.

## Role of the pharmacist cont.

- Focus on
  - ➔ Adverse drug reactions + drug interactions
    - avoidance
    - recognition / evaluation of clinical relevance
    - advice for management

# PATIENT CASE

Male patient, surgical department,  
K 4.01

	08:00	10:00	12:00	14:00	16:00	18:00	Mi 17.02.2016 (3)	Do 18.02.2016
Gewicht / Größe								
Kostform								
<b>Orale Medikation</b>								
Torem 10 mg								1
Carvedilol AL 12,5 mg		1						1
Atorvastatin Actavis 40 mg		1						
Pantoprazol Actavis 40 mg								1
Tamsulosin ratio 0,4 mg		1						
Novaminsulfon Lichtenst. 500...		2	2					2
Zopiclon Hexal 7,5 mg			1					
CitaLich 20 mg								1
Ebixa 10 mg								2
<b>Parenterale Medikation: Subkutan</b>								
Clexane 100 mg/ml			0,4 ml					0,4 ml
<b>Bedarfsmedikation</b>								
Sevredol 10 mg								
1 Tabl.; max. 4 Tabl./d								

## Neue Medikation

### Medikamentensuche

Bitte wählen Sie das zu verordnende Medikament aus.

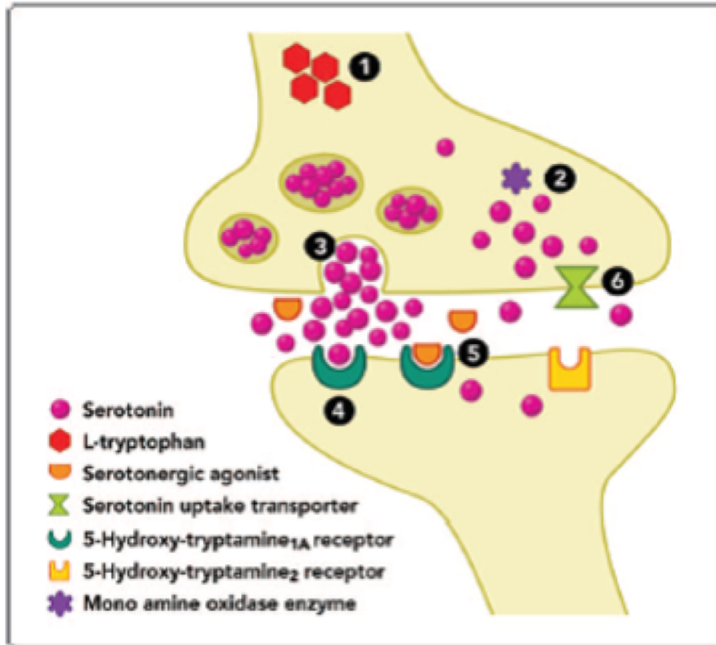
linez

Name	Darr.	Wirkstoff(e)
Linezolid-ratiopharm 600mg	Filmtabl...	Linezolid 600 mg
Zyvoxid 100mg/5ml	Trocke...	Linezolid 100 mg



# Serotonin syndrome caused by pharmacodynamic interactions

Drugs involved and corresponding mechanisms implicated:



- 1 Increased synthesis**  
i.e. increase substrate: L-tryptophan
- 2 Decreased metabolism**  
*Monoamine oxidase inhibitors (MAOIs):*  
Phenelzine, Tranylcypromine, Moclobemide, Selegiline, Isocarboxazid, Linezolid, Methylene blue
- 3 Increased release:**  
Amphetamines, Cocaine, Fenfluramine, Sibutramine, Ecstasy, Phenanthrene Opioids (Oxycodone, buprenorphine), Tramadol
- 4 Serotonin (5-hydroxy-tryptamine) receptor agonism:**  
Buspirone, Lysergic acid diethylamide (LSD), Di-hydro ergotamine (DHE), Triptans, Mirtazapine
- 5 Increased serotonin (5-hydroxy-tryptamine) receptor sensitivity:**  
Lithium
- 6 Decreased reuptake:**  
*Tricyclic Antidepressants (TCAs):*  
Amitriptyline, Imipramine, Clomipramine, Desipramine, Doxepin  
*Selective serotonin reuptake inhibitors (SSRIs):*  
Paroxetine, Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram  
*Serotonin noradrenaline reuptake inhibitors (SNRIs):*  
Venlafaxine, Duloxetine, Milnacipran  
*Other Antidepressants:*  
Trazodone, Nefazodone  
*Opioids:*  
Fentanyl, Methadone, Meperidine, Dextromethorphan, Tramadol  
*Miscellaneous:*  
Ondansetron, Granisetron, St. John's Wort

Fig. 1. Increase intrasynaptic serotonin levels: Mechanisms and associated serotonergic agents.

# Clinical relevance of drug interaction

**Table 3. Incidence of Serotonin Toxicity Associated with Use of Linezolid Plus Other Serotonergic Agents<sup>8,14,15,18</sup>**

Reference	Linezolid/ Serotonergic Agent, N	Serotonin Toxicity, n	Incidence, %
Butterfield (2012) <sup>14</sup>	2208	12 <sup>a</sup>	0.54
Go (2010) <sup>15</sup>	24	1 <sup>b</sup>	4.17
Lorenz (2008) <sup>8</sup>	53	1 <sup>b</sup>	1.89
Taylor (2006) <sup>18</sup>	72	2 <sup>a</sup>	2.78

<sup>a</sup>Serotonin toxicity diagnosed via Hunter Serotonin Toxicity Criteria or Sternbach's criteria.  
<sup>b</sup>Serotonin toxicity diagnosed via Hunter Serotonin Toxicity Criteria.

- 32 case reports, 3 with lethal outcome
- 69% with SSRI
- After a median of 60h

Woytowish MR, Maynor LM. Ann Pharmacother 2013; 47: 388-97

Karkow DC, et al. 2017 (retrospective case-control study, monocenter):  
no significant difference in incidence of serotonin syndrome  
linezolid alone or in combination with an SSRI or SNRI

J Clin Psychopharmacol 2017; 37: 518-23

# Management of drug interaction

- FDA: recommends wash out phase of 2 weeks (fluoxetine: 5 weeks)
  - Emergency situations: stop SSRI, monitor patient closely  
FDA drug safety communication, 10-20-2011
- Ramsey TD, et al. Ann Pharmacother 2013; 47: 543-60:  
„If coadministration of linezolid and a serotonergic agent cannot be avoided, clinicians should be aware of the symptoms and management of serotonergic toxicity, close monitoring is recommended and additional serotonergic agents should not be used.“



## Role of the pharmacist cont.

- Focus on
  - ➔ Surveillance of antibiotic consumption

Goal in European guideline:  
harmonized methodology ⇒ internationally  
comparable information on consumption



# Methodologies for reporting antibiotic consumption

## Approaches:

- Absolute values (e.g. units, weight)

	units	mg per unit
FLUCLOX STRAGEN 2G 1X10 IFL	10	2000
FLUCLOX STRAGEN 1G 1X10 IFL	10	1000
IMP-FLUCLOXACILLIN 1G 1X10 DFL	10	1000

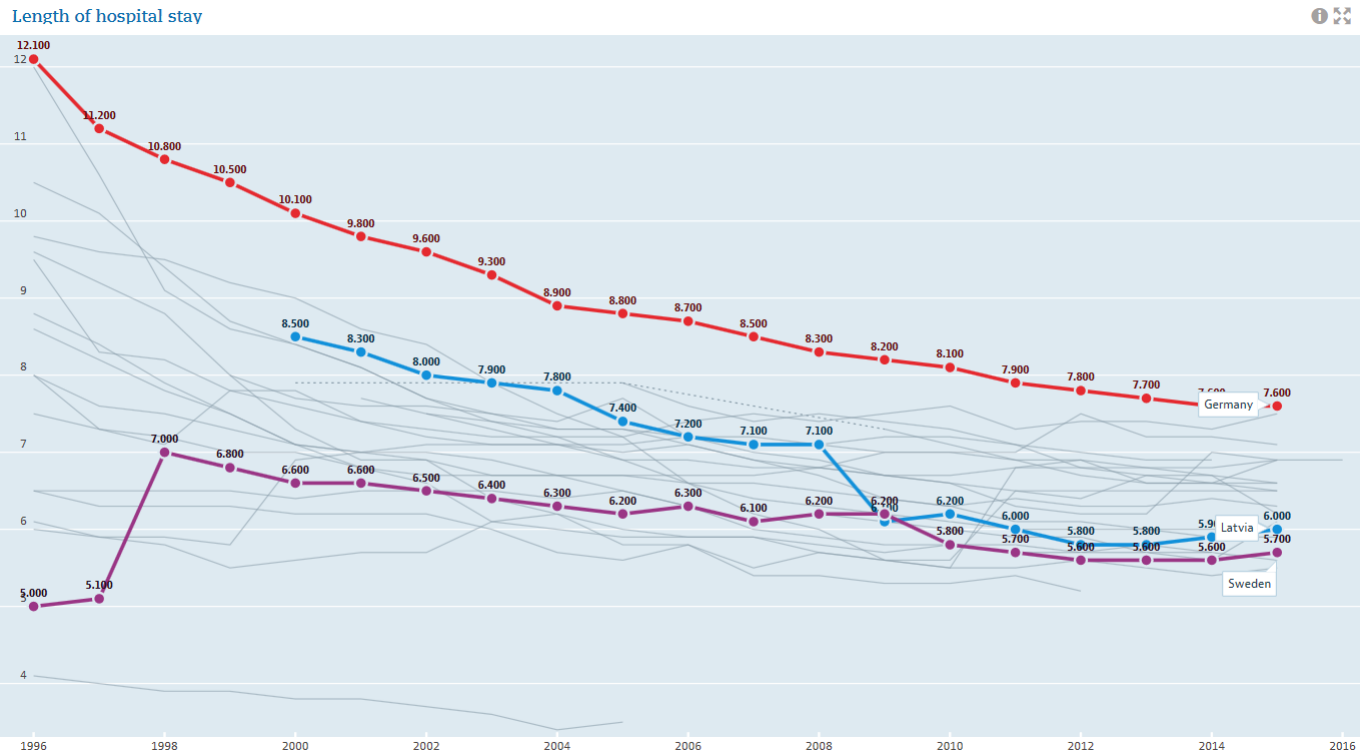
- Daily doses

- Easier to interpret, but not yet ideal
- PDD: prescribed daily dose
- DDD: defined daily dose (by WHO)
- Others (e.g. in Germany RDD: recommended daily dose)



e.g.  
230g  
flucloxacillin

# Development of acute care days (EU, 1996-2015)



<https://data.oecd.org>

# Methodologies for reporting antibiotic consumption cont.

To minimize bias by developments in length of hospital stays:

➔ **Reporting of densities is preferred**

Number of PDD / RDD / DDD

- Per 100 cases
- Per 100 days of inpatient care

➔ Input from administration / controlling is essential

# Example for regulation



## Bekanntmachungen - Amtliche Mitteilungen

Bundesgesundheitsbl 2013 · 56:996–1002  
DOI 10.1007/s00103-013-1780-8  
© Springer-Verlag Berlin Heidelberg 2013

Bekanntmachung des Robert Koch-Instituts

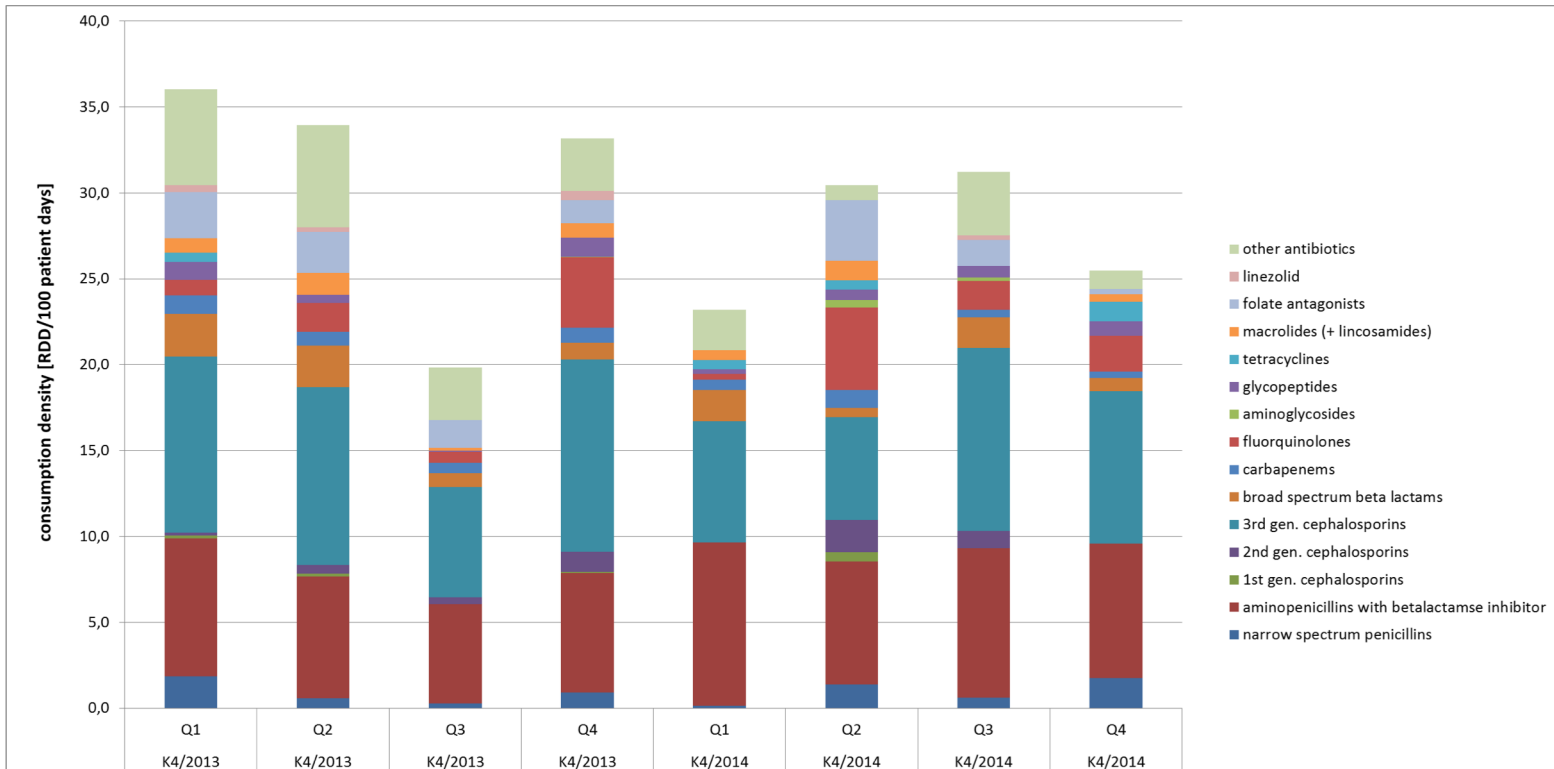
## Festlegung der Daten zu Art und Umfang des Antibiotika-Verbrauchs in Krankenhäusern nach § 23 Abs. 4 Satz 2 IfSG

Vom RKI gemäß § 4 Abs. 2 Nr. 2b zu erstellende Liste über die Daten zu Art und Umfang des Antibiotika-Verbrauchs<sup>1</sup>

- To be reported as antibiotic consumption per 100 inpatient days
- Level of differentiation is delineated, e.g. ICUs vs. Normal wards have to be reported separately
- To be reported & analyzed at least once per year (mandatorily)

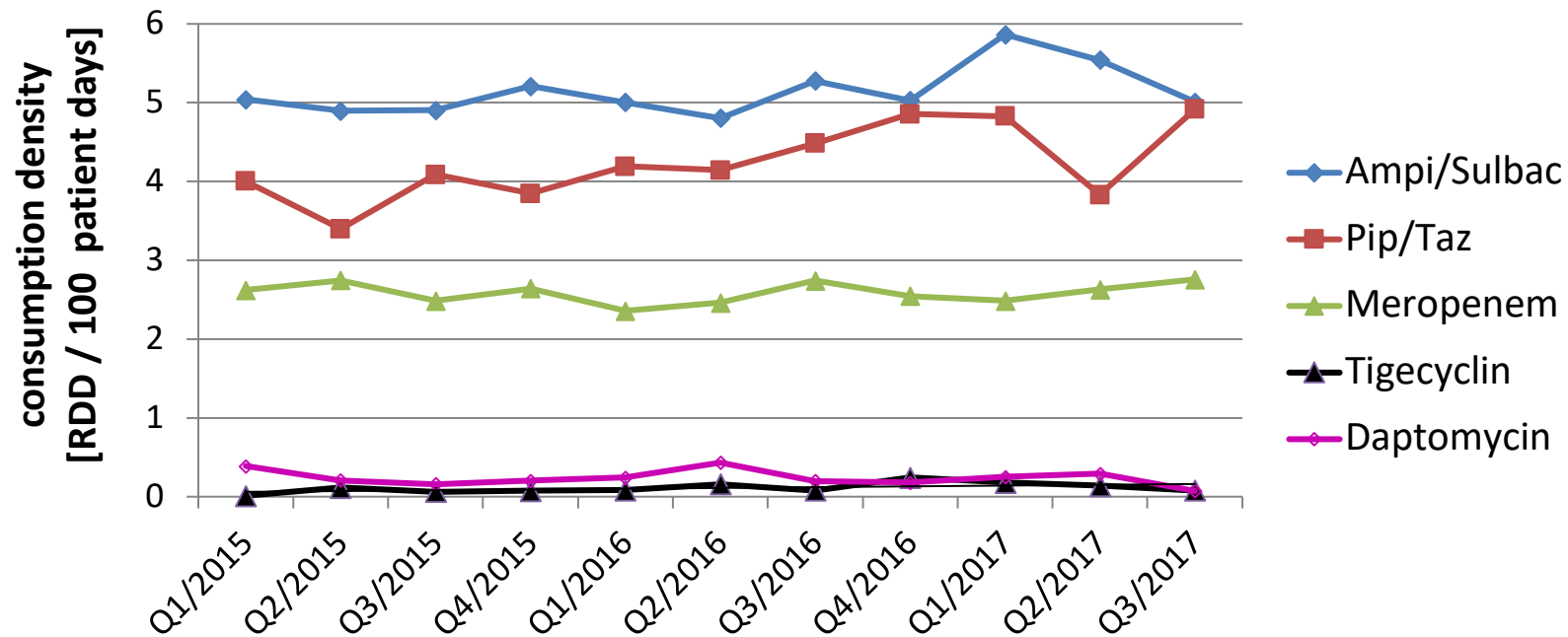


# Representation of data



...as tabular overview or graphically, e.g. stacked columns

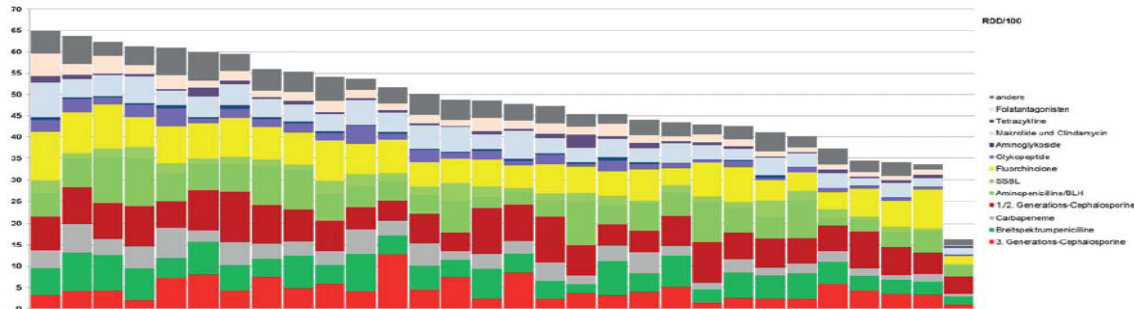
# Graphic representation of data



...as trends may facilitate interpretation

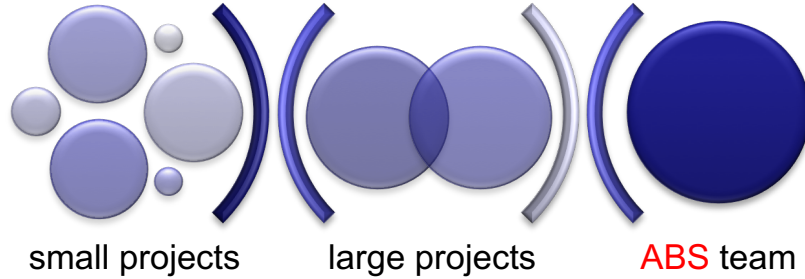
# Interpretation of antibiotic consumption data

- Has to be done
  - ➔ together with prescriber
  - ➔ taking into account local resistance data
- Benchmarking data may help



[http://www.antiinfektiva-surveillance.de/files/kvr\\_2014-2015\\_adka-if-dgi\\_121116\\_v.4\\_open\\_access\\_geschwaerzt\\_neu.pdf](http://www.antiinfektiva-surveillance.de/files/kvr_2014-2015_adka-if-dgi_121116_v.4_open_access_geschwaerzt_neu.pdf)

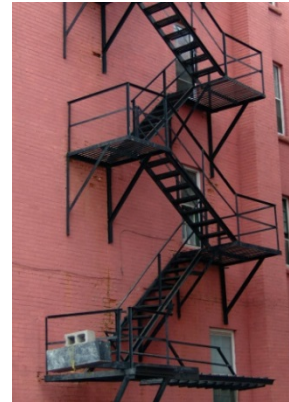
## Where to start?



## ALWAYS...

...build upon

- existing structures
- established cooperation



# Low-hanging fruits?

- Most obtainable targets... based on
  - Impact of problem
  - Severity of problem
  - Availability of (evidence based) interventions
  - Possible impact of interventions

Cox JA, et al. Clin Microbiol Infect 2017; 23: 812-8

- Customize intervention on basis of
  - Local issues
  - Resources
  - Expertise

Gaff DA, et al. Lancet Infect Dis 2017; e56-e63



LinkedIn.com

## **EIGHT KEY STEPS** for implementing an **Antimicrobial Stewardship Program (ASP)**

- 1** Assess the motivations
- 2** Ensure accountability and leadership
- 3** Set up structure and organization
- 4** Define priorities and how to measure progress and success
- 5** Identify effective interventions for your setting
- 6** Identify key measurements for improvement
- 7** Educate and Train
- 8** Communicate



<http://bsac.org.uk/wp-content/uploads/2013/07/Stewardship-Booklet-Practical-Guide-to-Antimicrobial-Stewardship-in-Hospitals.pdf>

## Self-assessment questions

- According to the EU guideline, only clinicians and microbiologists are key members of an ABS team

NO

- Prolonged infusions are advantageous for time-dependent antibiotics in the ICU setting

YES

- Antibiotic consumption data should be reported as densities

YES



<http://www.computerweekly.com>

- Hospital pharmacists are key team members of ABS teams
- Appropriate training is necessary
- Get started (with small projects)



Thank you for your attention!

Questions?  
Comments?



# Therapeutic drug monitoring

- To confirm / optimize dosing strategies
  - especially for challenging scenarios

