

Universitätsklinikum Würzburg 

Antimicrobial Stewardship Adaptable for Antifungal Agents?

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Disclosure

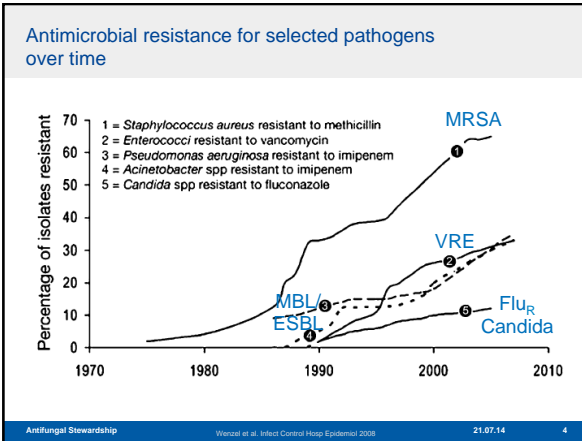
- 1. Employment or Leadership Position**
None
- 2. Advisory Role**
Basilea, Pfizer, MSD, Astellas, Gilead, Aicuris
- 3. Stock Ownership**
None
- 4. Honoraria**
Astellas, Gilead, MSD, Astellas, and Pfizer
- 5. Financing of Scientific Research**
Astellas, Gilead, MSD, Astellas, Pfizer, and BioCryst
- 6. Expert Testimony**
None
- 7. Other Financial Relationships**
none

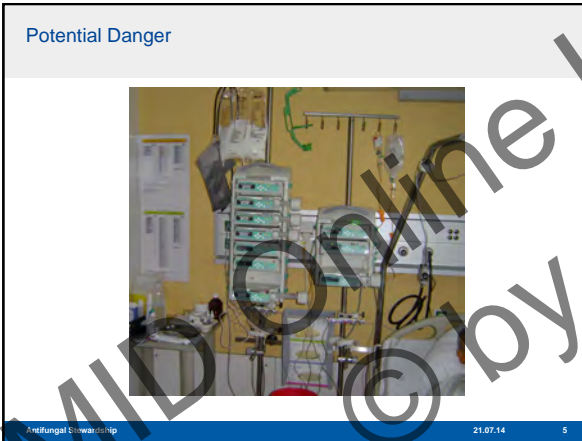
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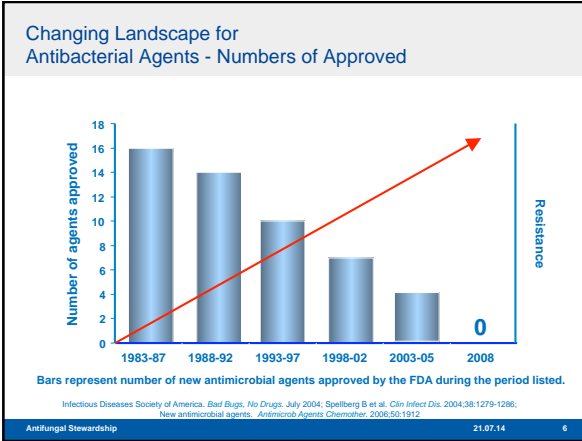
The Challenge



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Philosophy of Antimicrobial Therapy

- "Would like to feel good (physician)": **Good intention**
- "More is better...": **Inadequate dosing**
- "To be on the safe side": **Inadequate prophylaxis (duration, indication)**
- "To cover the patient...": **Multiple substances**
- "Need for a prescription": **Patients are demanding drugs**
- "Would treat in any case": **Costs and missing diagnostic procedures**
- "Expensive is better": **Concerns about resistance**
- "I know my antibiotics...": **Missing knowledge**
- Educated by drugs reps (**Too many visits by reps**)

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Dennis Maki 1998

"The development of new antibiotics without having mechanisms to ensure their appropriate use is much like supplying your alcoholic patients with a finer brandy."



Dennis G. Maki, MD
Faculty, University of Wisconsin
School of Medicine and Public Health

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Antimicrobial Stewardship

- Programms: „Antibiotic stewardship“, „Management“, „Control“, original idea „Partnership in Infection Control“
- US-Data: 60% of the patients receive antibiotic therapy 50% were not necessary.
- Antimicrobial substances: responsibly for 30% of the costs for medication
- Focus of the programs:
 - *Quality*
 - *Finance*
 - *Resistance development*

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Infection Control



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Antimicrobial Stewardship – Infection Control

Antimicrobial stewardship is aimed to limit the (unnecessary) use of broad spectrum antibiotics

Infection control is closely related to antimicrobial stewardship programs, as it is aimed to prevent the spread of resistant organisms that are still likely to emerge, despite maximal efforts

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Collateral damage of broad spectrum antimicrobial therapy

- ▶ Emerging resistance
- ▶ C. difficile infections
- ▶ Fungal infections
 - Chronic disseminated candidiasis
Sallah et al Cancer 2001
 - Duration of neutropenia of 15 days or longer OR, 11.7; 95% CI, 3.04-45 and
 - Quinolone prophylaxis OR, 3.85; 95% CI, 1.11-13.4
 - Candidemia
Das et al Int J Infect Dis 2011
 - Use of broad-spectrum antibiotics (92%), the presence of an intravascular device (IVD) (82%)

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Triazole resistance

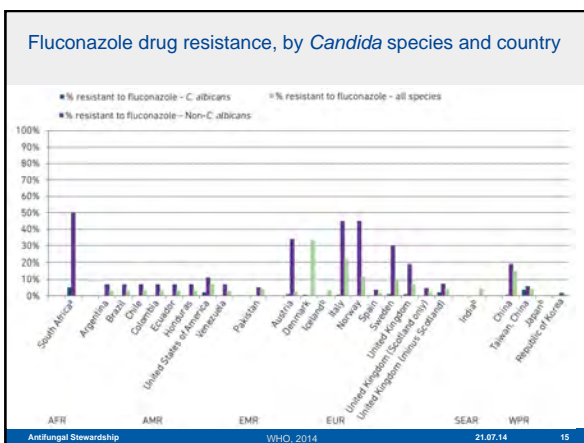
- ▶ in *Aspergillus fumigatus*
 - both azole-naïve
 - azole-exposed patients
- ▶ mostly in patients with cavitary disease
- ▶ allergic aspergillosis
- ▶ cancer patients with invasive aspergillosis

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Candida species - Resistance

- ▶ Largely applies to fluconazole
- ▶ Lesser extent: Echinocandins
- ▶ Longitudinal data from laboratory surveillance shows that fluconazole resistance amongst *Candida albicans* and *Candida parapsilosis* is uncommon,
- ▶ *Candida glabrata* resistance may exceed 15%
- ▶ Breakthrough candidaemia on caspofungin therapy has been documented in 2.4% of patients
 - associated with prolonged therapy when source control of sepsis was not achieved

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Antifungal Therapy: Opportunities of Improvement

- ▶ The challenges of de-escalation
- ▶ Restraining empiric antifungal use relies on improved diagnostics
- ▶ Measuring the performance of an AFS programme:
 - *Quality and quantity of prescribing*
 - *Process and outcome measures*

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Principles of Stewardship

- ▶ Optimizing the use of currently available antifungal agents
 - *high cost*
 - *attendant toxicities*
 - *focus on haematology–oncology patients because they are high users of antifungal agents*
- ▶ Established record of practice guidelines, but the principles discussed are applicable to other high users:
 - *intensive care unit (ICU) and*
 - *solid-organ transplant (SOT) recipients.*
 - *Implementation and computerized decision-support systems (CDSSs) along with engagement with end-users and institutional stakeholders.*

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Essential Elements of an Antifungal Stewardship Program

- ▶ Implementation of antifungal guidelines
- ▶ Guidelines adapted to the local context
 - *Many national and international guidelines for the management of patients with IFDs providing appropriate evidence-based care.*
 - *Although little is known about their impact on provider behaviour,*
- ▶ Preprescription approval with postprescription review and feedback
 - *Restrictive interventions such as formulary restriction and preprescription approval are more than three times more influential than persuasive interventions, such as education, on prescribing behaviour*

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Principles of Stewardship
The Team

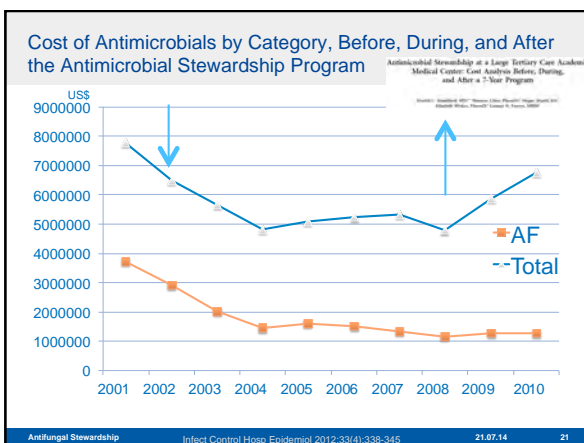
- ▶ Infectious Diseases trained physician
- ▶ Microbiologist
- ▶ (Ideally ID-trained) pharmacist
- ▶ IT-expert

Titel der Präsentation 21.07.14 19

Costs

- ▶ Antifungal agents contribute 7–15% of total treatment costs of patients with IFDs
- ▶ Haematology–oncology patients; pharmacy costs accounted for 64% of the difference in mean hospital cost per patient
- ▶ Antifungal agents accounted for 27% of the overall difference ($P < 0.001$) with no significant differences seen in ward costs between infected and uninfected controls (27%, $P = 0.091$)
- ▶ The proportion of pharmacy (60%) to ward (31%) costs persisted at 12 weeks follow-up, suggesting that the finding was robust

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Defined Daily Doses per 1,000 Patient-Days of Selected Antimicrobials

	During program					After program	
	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010
Total antibacterials	1,174	1,023	1,023	990	851	868	867
Antifungals	150	129	129	123	120	139	142
Fluconazole	78	63	66	61	69	71	66
Voriconazole	28	22	27	24	25	31	29
Caspofungin	4.6	9.1	5.7	7.2	0.4	0.4	0.4
Micafungin	0	0	2.2	9.2	14	23	31
Total antivirals	142	99	125	116	63	79	81
Total antimicrobials	1,512	1,303	1,321	1,272	1,073	1,125	1,129

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- Conclusions from the USA
- ▶ ASP with a preauthorization protocol using a "BUGS" beeper
 - ▶ AMT to assure appropriate use, and computer decision-support assistance was an extremely cost-effective model for antimicrobial stewardship over a period of 7 years
 - ▶ Discontinuation has proven to be very costly
 - ▶ ASP restarted, but an automatic infectious diseases consult has replaced the preauthorization requirement for "restricted" antimicrobials.
- Antifungal Stewardship Infect Control Hosp Epidemiol 2012;33(4):338-345 21.07.14 23

- Demonstrating the continued benefit of an AFS program
Prevention and management of IFDs.
- ▶ hospital administrators, drug committees and senior clinicians
 - ▶ monitoring of:
 - process
 - outcome
 - structural measures
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Performance measures for an AFS program (I)
Process measures (I)

Characteristic	Comments
Antifungal drug consumption	Information on appropriateness of therapy
	Measured in defined daily doses, prescribed daily doses or days of therapy adjusted for bed occupancy
	Large fluctuations in small populations (e.g. the ward level), because of the effect of outlier patients

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Performance measures for an AFS program (II)
Process measures (II)

Characteristic	Comments
Minimum standards of prescribing	
Documentation of treatment rationale	The reason(s) for prescription should be recorded in the medical record
Dose optimization using therapeutic drug monitoring (TDM)	Resources should be available to ensure that the pharmacokinetic/ pharmacodynamic endpoints proposed for voriconazole which optimize clinical efficacy and minimize toxicity are rapidly attained
	The utility of TDM for posaconazole is unclear
	TDM for itraconazole is well established

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Performance measures for an AFS program (III)
Process measures (III)

Characteristic	Comments
Therapeutic streamlining	
De-escalation of empiric antifungal therapy	Assisted by the high negative predictive value of NCBTs such as galactomannan and Aspergillus PCR in the appropriate clinical context
	Best studied in neutropenic patients
De-escalation from broad to narrower spectrum drugs	Guided by susceptibility results and clinical response
Intravenous to oral switch therapy	Can decrease health-care costs/ adverse events without compromising outcomes
	Suitable for agents with high oral bioavailability, for example, voriconazole

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Performance measures for an AFS program (IV)
Process measures (IV)

Characteristic	Comments
Timeliness and completeness of diagnostic investigations when IFD suspected	Improved diagnosis to guide therapy, such as ceasing or modifying antifungal therapy
Concordance of prescribing with institutional guidelines using an indication-driven approach	Clinical audit can be a labour-intensive process requiring chart review, online tools, for example, computerized decision support system or point prevalence surveys. May be best performed targeting areas where there is reasonable quality evidence and/or institutional guidelines, for example, antifungal prophylaxis in patients with AML undergoing intensive chemotherapy or use of empiric antifungal therapy Includes timeliness, appropriateness and adequacy of initial antifungal therapy

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Performance measures for an AFS program (V)
Outcomes measures (I)

Characteristic	Comments
IFD incidence in targeted groups	Targeted surveillance of patients at highest risk for IFDs, that is, allogeneic HSCT recipients and patients with AML undergoing chemotherapy for initial remission, refractory or relapsed disease. Requires prospective surveillance Evolves in response to changing practices, for example, formulary changes Candidemia in the ICU

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Performance measures for an AFS program (VI)
Outcomes measures (II)

Characteristic	Comments
Antifungal drug expenditure	Patient quality and safety initiatives encompass AFS programmes and should not be driven by cost Subject to fluctuations in purchase contracts, formulary changes, variations in ordering Targeting specific high-cost drugs, for example, liposomal amphotericin, intravenous voriconazole, echinocandins, is an efficient means of demonstrating value of an AFS programme

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Performance measures for an AFS program (VII)
Structural measures

Characteristic	Comments
Structural measures	At a minimum includes an antifungal drug policy or locally adapted practice guidelines

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Planning an Antimicrobial Stewardship

- ▶ Multi- and interdisciplinary approach
 - ▶ 0,5 full time position for every 250 hospital bed
- ▶ Availability of data: Microbes, resistance, and antiinfective usage
 - ▶ Interpretation by AMS team
 - ▶ Quality indicators
 - ▶ Use of local SOP, antiinfectives list, restrictions
- ▶ Design and implementation of training courses, training and information
- ▶ Interdisciplinary ID rounds (proactive prescription analysis)
- ▶ Complimentary strategies (e.g.)
 - ▶ De-escalation
 - ▶ Duration
 - ▶ Oral switch
 - ▶ Transmission of information
 - ▶ MR-Management

2014: S3-Leitlinie: Strategie zur Steigerung rationaler Antibiotika-Anwendung im Krankenhaus, AWMF-Registernummer 092/001
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Beispiel für eine Antibiotika-Hausliste

Antibiotika (AB)-Gruppe	Appl.	Handelsname	Wirksubstanz	Durchschnittliche Tagesdosis Normale Nierenfunktion CrCl > 80 ml/min	Eingeschränkte Nierenfunktion CrCl 30-80 ml/min	TTK
Penicilline	i.v.	Infectocillin	Benzylpenicillin	3 x 10 Mio IE oder 4 x 5 Mio IE	2 x 10 Mio IE	€€
	oral	Penicillin V 1 Mogip	Phenoxymethylpenicillin	3 x 1 Mio IE	3 x 1 Mio IE	€
Aminopenicilline	i.v.	Ampicillin Amoxiclavat	Ampicillin Amoxicillin	3 x 2 g 3 x 1 g	2 x 2 g 3 x 1 g	€€ €
Aminopenicilline + Betaaktanamasehemmer	i.v.	Ampicil Subac Amocli gitas	Grün: Standard-AB		1000mg	€€
	oral				25 mg	€
Acylaminopenicilline	i.v.	Piperacil	Gelb: Reserve-AB			€€
Acylaminopenicilline + Betaaktanamasehemmer	i.v.	Piperacil Tazobac			g	€€
Carbapeneme	i.v.	Meropen	Rot: Spezial-AB, Rücksprache mit dem Oberarzt			g €€€€
Tetracycline	i.v. oral	Doxyl Doxylflexal Tetra	Doxycyclin	100-200 mg/Tag	Dosisanpassung notwendig	€ €
Aminoglykoside	i.v.	TubraCell Gentamicin	Tetracyclin Gentamicin	1 x 5-6 mg/kg KG 1 x 5 mg/kg KG	Rücksprache mit Oberarzt	€€ €€
Nitroimidazole	i.v. oral	Mitronidazol Metronidazol	Mitronidazol Metronidazol	3 x 500 mg 3 x 400 mg	3 x 500 mg 3 x 400 mg	€ €
Oxazolidinone	i.v. oral	Zyvoxid Zyvoxid	Linezolid Linezolid	2 x 600 mg 2 x 600 mg	2 x 600 mg 2 x 600 mg	€€€€ €€€€

2014: S3-Leitlinie: Strategie zur Steigerung rationaler Antibiotika-Anwendung im Krankenhaus, AWMF-Registernummer 092/001

Conclusion (I)



- ▶ IFDs have a lower incidence compared to multiresistant bacteria
- ▶ Economic burden is likely to increase over time
 - Institutional variation in incidence rates
 - Emerging but underrecognized antifungal resistance
 - New treatment practices
 - Knowledge of local epidemiology

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Conclusion (II)

- ▶ Cornerstone of AFS:
 - AFS team part of the ABS/AMS team: multidisciplinary team
 - Implementation of institutional guidelines which should largely accord with international or national standards
 - Implementation needs to be augmented by
 - Provider audit
 - Feedback
 - Quality use of medicine indicators
 - Performance measures
 - Engaging and consensus building with end-users is vital for mission success.
- ▶ AFS programs need to demonstrate value to hospital administrators and although a reduction in healthcare costs is regarded as a secondary goal of AMS

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“It was not enough to produce satisfactory soaps, it was also necessary to induce people to wash”

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