



Antibiotic stewardship programs – How do they promote a “safer” environment

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**Antibiotic stewardship programs:
How do they promote a “safer”
environment?**

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Disclosures

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OVERUSE

“The desire to ingest medicines is one of the principal features which distinguish man from the animals.”



Osler W: Aecquanimitas, 1920



What is antibiotic stewardship?

- An activity that optimizes antimicrobial management and includes selection, dosing, route and duration of antimicrobial therapy and prophylaxis
- A marriage of infection control and antimicrobial management
- Mandatory infection control compliance
- Selection of antimicrobials that do the least collateral damage, e.g., MRSA, ESBLs, *Clostridium difficile*

ESBL, extended-spectrum β -lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*
Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-177.

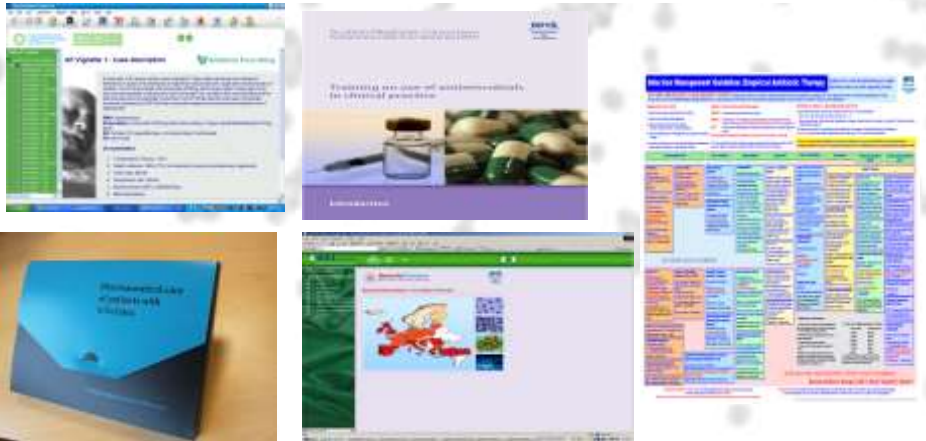


Antibiotic stewardship in Europe: European survey to investigate antibiotic policy criteria in 170 hospitals from 32 countries

- Only 57% of European hospitals surveyed have a written antibiotic policy; one-fifth of teaching hospitals do not
- Hospitals in northern and western Europe are most likely to convene antibiotic committees
- No differences in overall antibiotic use
- Policies and practices relating to antibiotic stewardship vary considerably across Europe
- New stewardship initiatives are necessary to achieve harmonization of recommended practices

Bruce J, et al. *J Antimicrob Chemother*. 2009;64(4):853-60.

ABS – Local aspects: Foundation doctors, staff induction, pharmacist training packs, guidelines



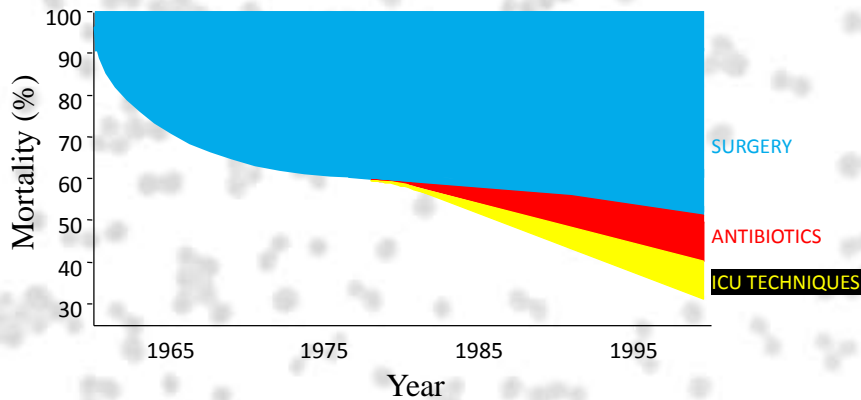
ABS, antibiotic stewardship.
With courtesy of Prof. Dilip Nathwani, OBE

ABS – General aspects

- Source control – necessary or unnecessary?
- Initiation of therapy – early vs. delayed?
- Diversity – first line vs. multiple substances?
- De-escalation – broad vs. narrow spectrum?
- Duration of therapy – how long to treat?
- Discontinuation of therapy – any markers?
- What are the early switch and early discharge strategies?

ABS, antibiotic stewardship.
Nathwani D, et al. *Clin Microbiol Infect.* 2014;20(10):993-1000; Eckmann C, et al. *Int J Antimicrob Agents.* 2014;44(1):56-64.

Prognosis of intra-abdominal infections: Importance of source control



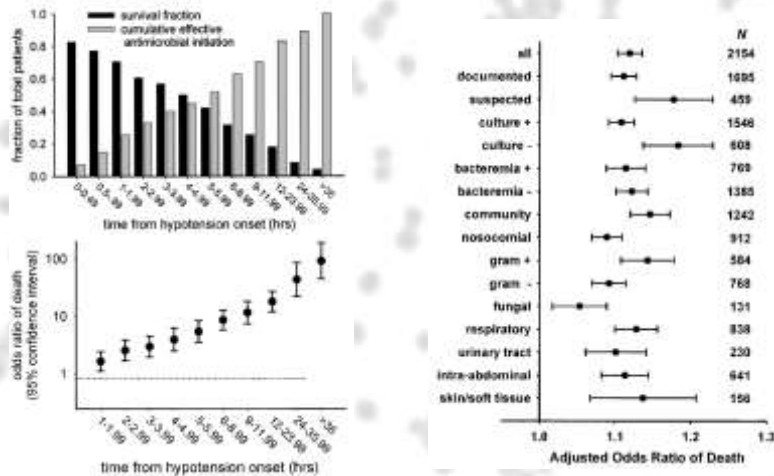
ICU, intensive care unit.
Adapted from: Wittmann DH. *Intra-Abdominal Infections*. Marcel Dekker Inc; Frankfurt 1991:8-9.

Treatment of peritonitis 1925



- “Very inconsistent therapy”
- Collective: n=25
- Mortality: 80% (!)
- “Improvement necessary”

Effect of early vs. delayed antimicrobial therapy in septic shock



Kumar A, et al. *Crit Care Med.* 2006;34:1589-1596.

“Aggressive” vs. “Conservative” approach to antibiotic therapy in hemodynamically stable surgical ICU patients

Bernhard et al. *Critical Care* 2014, **18**:671
<http://ccforum.com/content/18/6/671>



COMMENTARY

The early antibiotic therapy in septic patients - milestone or sticking point?

Michael Bernhard^{1*}, Christoph Lichtenstem², Christian Eckmann³ and Markus A Weigand²

“Aggressive” vs. “Conservative” approach to antibiotic therapy in hemodynamically stable surgical ICU patients



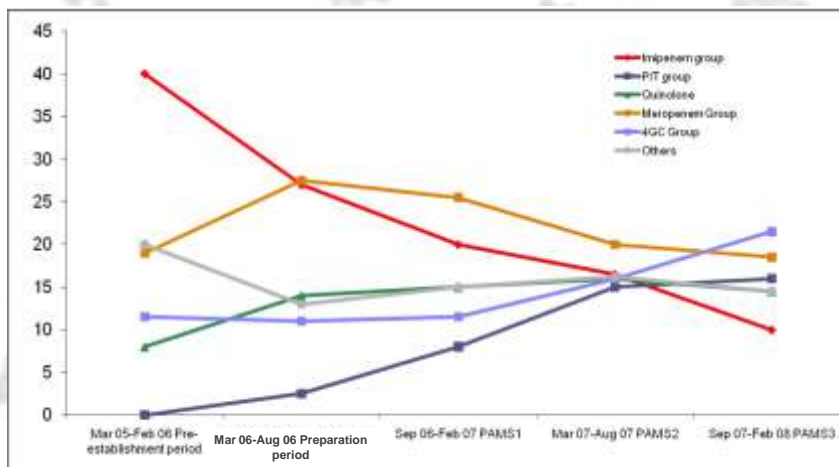
	Aggressive	Conservative	P
Total, n	762	721	
Infected, n (%)	101 (13)	100 (14)	ns
Appropriate	144/231 [62%]	158/214 [74%]	0.0095
Duration	17.7	12.5	0.008
Mortality, %	27	13	0.015
Adjusted mortality	OR 2.5 (95% CI 1.5-4.0)		

CI, confidence interval; ICU, intensive care unit; ns, non-significant; OR, odds ratio.
Hranjec T, et al. *Lancet Infect Dis.* 2012;12:774-780.

Antibiotic diversity

Pre-establishment and reparation period

PAMS

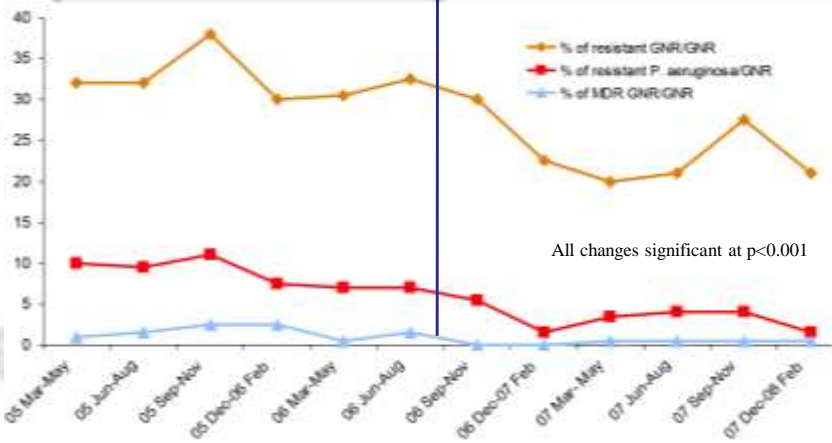


4GC, fourth generation cephalosporin; GNR, gram-negative rods; PAMS, periodic antimicrobial monitoring and supervision; P/T, piperacillin/tazobactam.
Takesue Y, et al. *J Hosp Infect.* 2010;75:28-32.

Antibiotic diversity

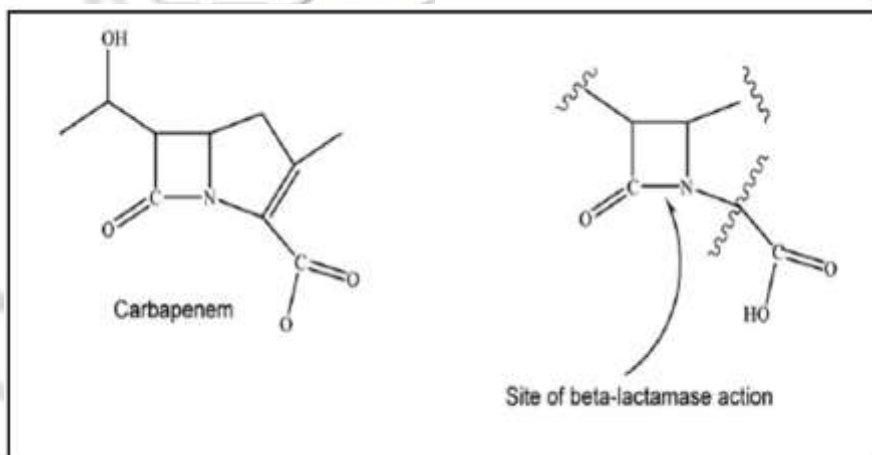
Pre-establishment and reparation period

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4GC, fourth generation cephalosporin; GNR, gram-negative rods; PAMS, periodic antimicrobial monitoring and supervision; P/T, piperacillin/tazobactam. Takesue Y, et al. *J Hosp Infect.* 2010;75:28-32.

save the **Carbapenems!**



love the earth

Treatment options for cIAI caused by ESBL-producing bacteria

Drug	Advantages	Disadvantages
Meropenem Imipenem/ Cilastatin	<ul style="list-style-type: none"> • High clinical success rates • Inexpensive 	<ul style="list-style-type: none"> • “Overuse” results in increased carbapenem resistance
Ertapenem	<ul style="list-style-type: none"> • High clinical success rates 	<ul style="list-style-type: none"> • Limited activity against <i>Pseudomonas</i> spp.
Piperacillin/ Tazobactam	<ul style="list-style-type: none"> • Favorable clinical response in recent trials • Well known and well tolerated 	<ul style="list-style-type: none"> • Varying susceptibility rates (around 70%) • Varying clinical success rates
Tigecycline	<ul style="list-style-type: none"> • Favorable clinical results in recent trials with severely ill patients • Broad range of activity against resistant rods 	<ul style="list-style-type: none"> • Increased mortality discussion • Lack of activity against <i>Pseudomonas</i> and <i>Proteus</i> spp.
Ceftolozane/ Tazobactam	<ul style="list-style-type: none"> • High clinical success in cIAI due to ESBL producers • Broad range of activity 	<ul style="list-style-type: none"> • Not yet licensed • Information on pricing yet to be confirmed

cIAI, complicated intra-abdominal infection; ESBL, extended spectrum β -lactamase.
Eckmann C, Solomkin J. *Expert Opin Pharmacother.* 2015;16:271-80.

What is your view on de-escalation of antibiotics?

1. I ♥ de-escalation! I always do it when I receive the microbiological report.
2. I never do it because it is not proven to be safe!
3. It is not safe for polymicrobial infections.
4. I don't trust culture results to give definitive proof of the absence of additional microorganisms, e.g., MDR.



De-escalation: The “evidence”

Main results

- 436 references.
- No randomized controlled trials testing de-escalation could be included in this review.

Author’s conclusions

- No adequate, direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock.
- Not possible to either recommend or not recommend the de-escalation of antimicrobial agents in clinical practice for septic patients.
- This uncertainty warrants further research via randomized controlled trials or cohort studies.

Gomes Silva BN, et al. *Cochrane Database Syst Rev.* 2010 Dec 8;(12):CD007934.

De-escalation in ICU?

- Design: Multi-center, non-blinded, randomized controlled trial, non-blinded,
- Collective: 59 patients continued (CON)
- Endpoints: Days with sepsis (2 days); days with sepsis
- Results I: Days with sepsis (2 days); days with sepsis
- Results II: More patients in DE (27% DE vs. 11% CON)
- Results III: More patients in DE (vs. 7.5 days, p=0.001)



Leone M, et al. *Intensive Care Med.* 2014;40:1399-1408.



Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial):

A multicenter, randomized, controlled trial

- Collective: n=621 patients, prospectively
- Mortality day 28: 21% PCT, 20% control
- Mortality day 60: 30% PCT, 27% control
- Days without AB: 14.3 vs. 11.6 days (p<0.0001)
- Exception: Surgical cohort!!!
- Conclusion: A PCT-guided strategy to treat suspected bacterial infections in non-surgical patients in ICU could reduce antibiotic exposure and selective pressure

AB, antibiotics; ICU, intensive care unit; PCT, procalcitonin
Bouadma L, et al. *Lancet*. 2010;375:463-474.



Procalcitonin: Kinetics fails to predict treatment response in secondary peritonitis with septic shock

- Collective: n = 101 patients
- Design: PCT on days 0,1,3,5 correlated with treatment success and outcome
- Results: 50% of patients with treatment success still had elevated PCT-values
40% of patients with an 80% PCT reduction had treatment failure

PCT, procalcitonin.
Jung B, et al. *Crit Care*. 2013;17:R255

Procalcitonin: Kinetics fails to predict treatment response in secondary peritonitis with septic shock



Eckmann and Sanchez-Garcia *Critical Care* 2013, 17:1017
<http://ccforum.com/content/17/6/1017>



COMMENTARY

Monitoring treatment response in abdominal sepsis with procalcitonin - if only!

Christian Eckmann^{1*} and Miguel Sanchez-Garcia²

INVITED ARTICLE

CLINICAL PRACTICE

Elise J. C. Goldstein, Section Editor

Is the “Low-Hanging Fruit” Worth Picking for Antimicrobial Stewardship Programs?

Debra A. Goff,¹ Karri A. Bauer,¹ Erica E. Hoed,¹ Kurt B. Stevenson,^{2,3} Jeremy J. Taylor,¹ and Jessica E. West²

¹Department of Pharmacy, The Ohio State University Wexner Medical Center, ²Division of Infectious Diseases, College of Medicine, and ³Division of Epidemiology, College of Public Health, The Ohio State University, Columbus


A new antimicrobial stewardship program can be overwhelmed at the breadth of interventions and education required to conduct a successful program. The expression “low-hanging fruit,” in reference to stewardship, refers to selecting the most obtainable targets rather than confronting more complicated management issues. These targets include intravenous-to-oral conversions, batching of intravenous antimicrobials, therapeutic substitutions, and formulary restriction. These strategies require fewer resources and less effort than other stewardship activities; however, they are applicable to a variety of healthcare settings, including limited-resource hospitals, and have demonstrated significant financial savings. Our stewardship program found that staged and systematic interventions that focus on obvious areas of need, that is, low hanging fruit, provided early successes in our expanded program with a substantial cumulative cost savings of \$832 590.

Goff DA, et al. *Clin Infect Dis*. 2012;55(4):587-592.

Do you have an intravenous to oral switch protocol in your hospital?

1. Yes
2. No
3. Don't know
4. Don't care





ES/ED criteria

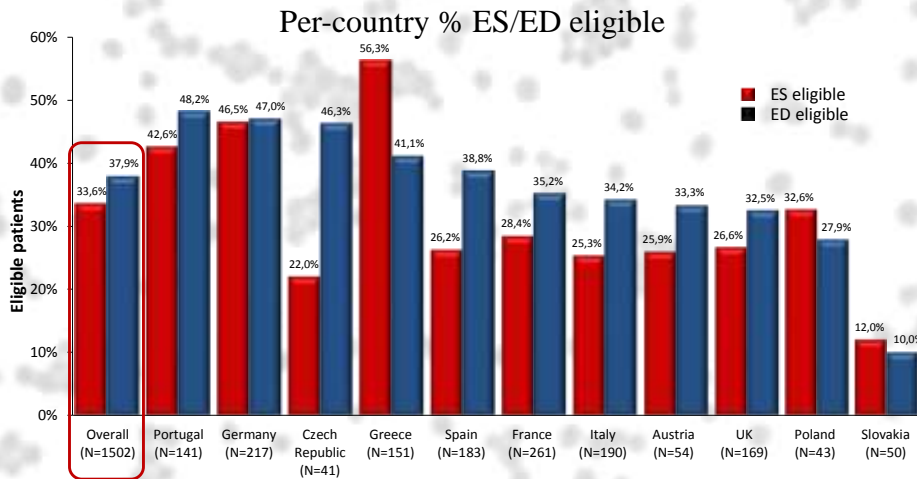
- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study; inclusive of Desai¹ and Parodi² criteria
- The key (essential) criteria were selected by KOLs and used to estimate ES/ED hypothetical opportunities

ES	Stable clinical infection²	Afebrile / temperature <38°C for 24 hours^{1,2}	WBC count normalizing (WBC 4-12 × 10⁹/L)^{1,2}	ED
	No unexplained tachycardia¹	Systolic BP ≥100 mmHg³	Patient tolerates oral fluids / diet^{1,2}	
		No other reason to stay in hospital except infection management²		

BP, blood pressure; ED, early discharge; ES, early switch; WBC, white blood cell; KOL, key opinion leader
 1. Desai M, et al. *BMC Infect Dis.* 2006;6:94; 2. Parodi S, et al. *J Manag Care Pharm.* 2003;9:317-26; 3. Nathwani D, et al. *Clin Microbiol Infect.* 2014 Oct;20(10):993-1000.



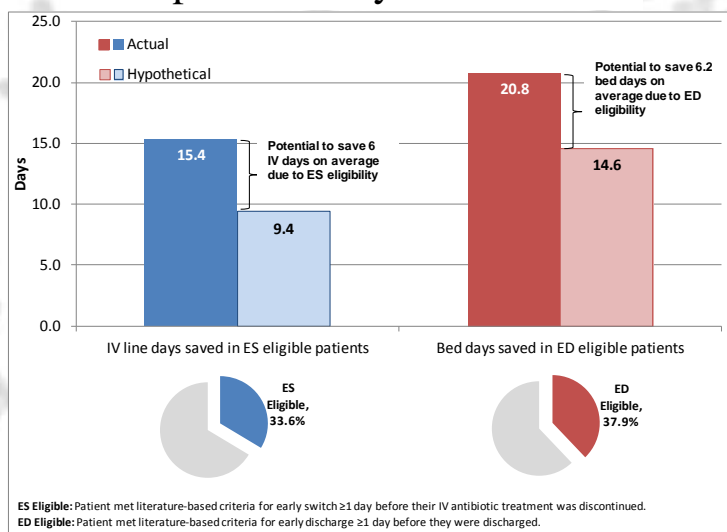
Key results: Country level ES/ED opportunities



ED, early discharge; ES, early switch.
Eckmann C, et al. *Int J Antimicrob Agents.* 2014;44:56-64



Early switch and early discharge potential days saved



ES Eligible: Patient met literature-based criteria for early switch ≥ 1 day before their IV antibiotic treatment was discontinued.
ED Eligible: Patient met literature-based criteria for early discharge ≥ 1 day before they were discharged.

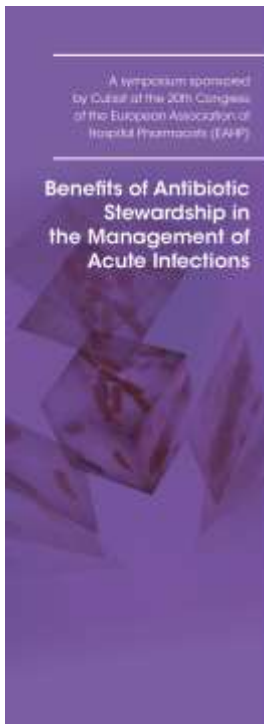
ED, early discharge; ES, early switch
Nathwani D, et al. *Clin Microbiol Infect.* 2014;20:993-1000

Antibiotic stewardship: Conclusion

- Don't forget possible source control!
- Early initiation is indicated in severely ill patients
- Diversity might be a useful tool against selective pressure
- The value of de-escalation still needs to be determined
- Procalcitonin does not always help for discontinuation of therapy (mostly, 7 days of therapy is enough)
- Early switch and early discharge strategies can be beneficial for patients and for the hospital
- Overcome barriers for implementation of antibiotic stewardship

Implementation of antibiotic stewardship:





Agenda

12:00	Chairman's welcome and introduction	Jonathan Cooke <i>Manchester, UK</i>
12:20	Antibiotic stewardship programs – How do they promote a "safer" environment	Christian Eckmann <i>Hannover, Germany</i>
12:40	Intravenous to oral switching, OPAT, and early discharge	Mark Gilchrist <i>London, UK</i>
13:00	The role of new antibiotics in the treatment of severe infections – Safety and efficacy features	Christian Eckmann <i>Hannover, Germany</i>
13:15	Q&A with panel discussion	All