Novel therapies & the role of early switch and early discharge protocols for management of MRSA infections

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Infections Due to MRSA: Walking a Fine Line to Meet Real World Expectations

Integrated symposium sponsored by MSD

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Disclosures

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- Non-profit Institutions (grants):
  - the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  - The European Union for applied research on optimization of β-lactams treatments through on-line monitoring of free serum levels
  - *Université catholique de Louvain* for past personal support

- Industry (grants, PPPs, and honoraria):
  - AstraZeneca, Bayer, Cempra, Debiopharm, Eumedica, GSK, Melinta, Merlion, MSD, Northern Antibiotics, Trius …

Slides: http://www.facm.ucl.ac.be → Lectures

The programme…

- Novel therapies …
- Old vancomycin ?
- Treatment duration …
- Early switch / Early discharge is possible…
- Do we have criteria ?
- What do we save ?
- Sum up … and questions, suggestions, objections …

The programme…

really novel ?

- **Novel therapies …**
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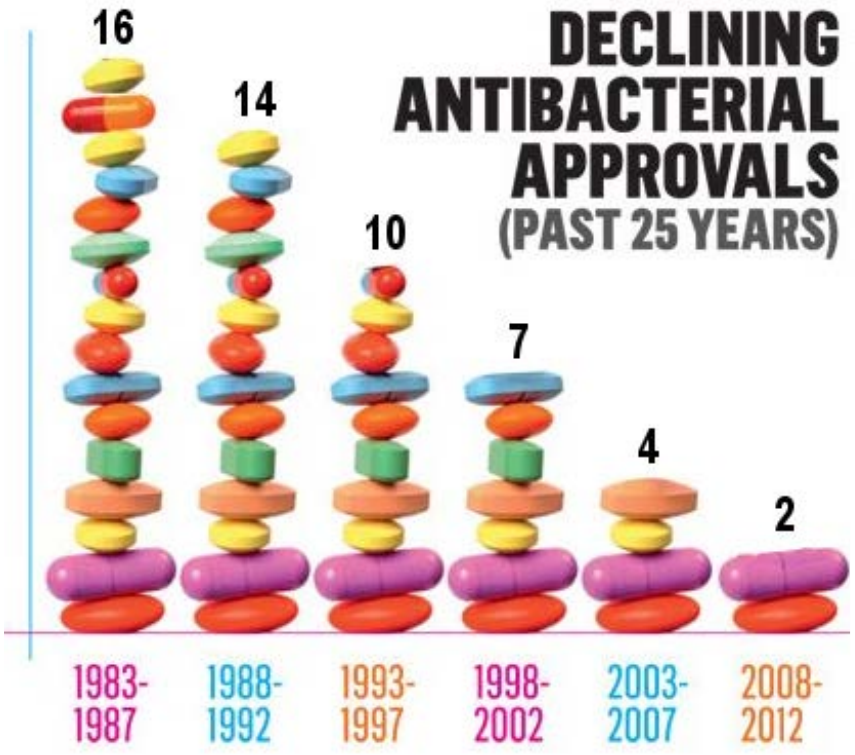
New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



telavancin

ceftaroline

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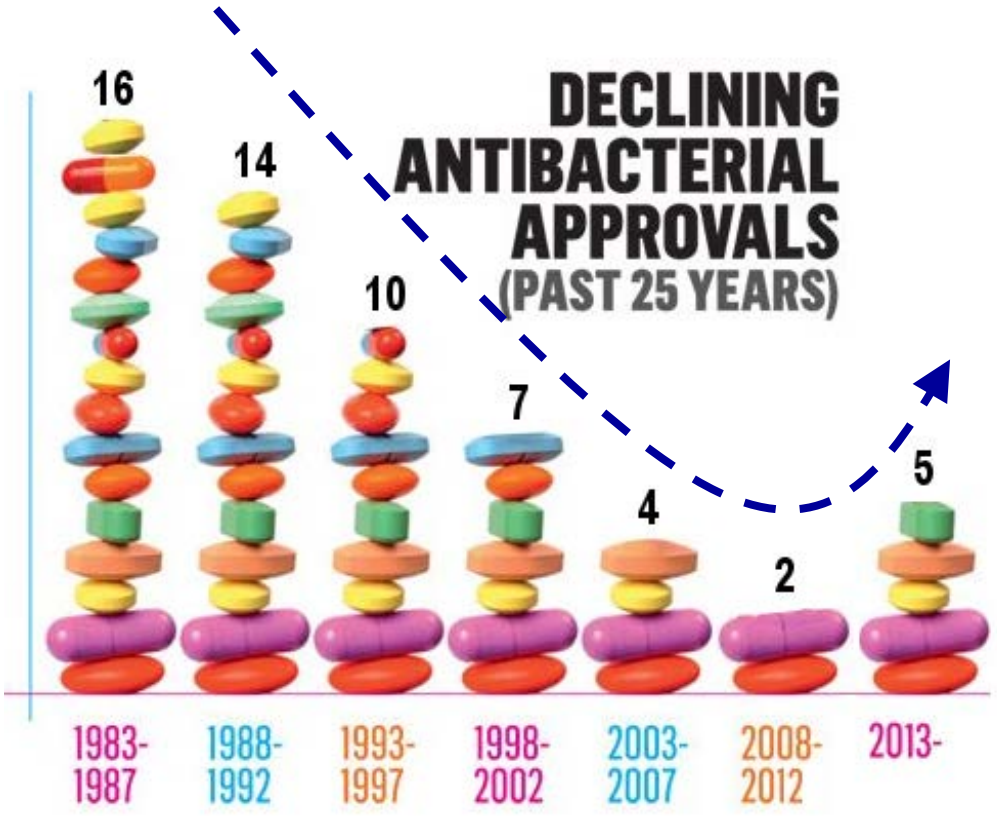


Shall we succeed ?

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- ceftaroline

Where do we go from here …

- Do we need new anti-MRSA drug ?

  - "*Because of the virtual epidemic of MRSA infections worldwide, severe soft tissue infections should be treated with agents that have high level activity against these strains. Local antibiograms are thus crucial for rational treatment.*" [1]

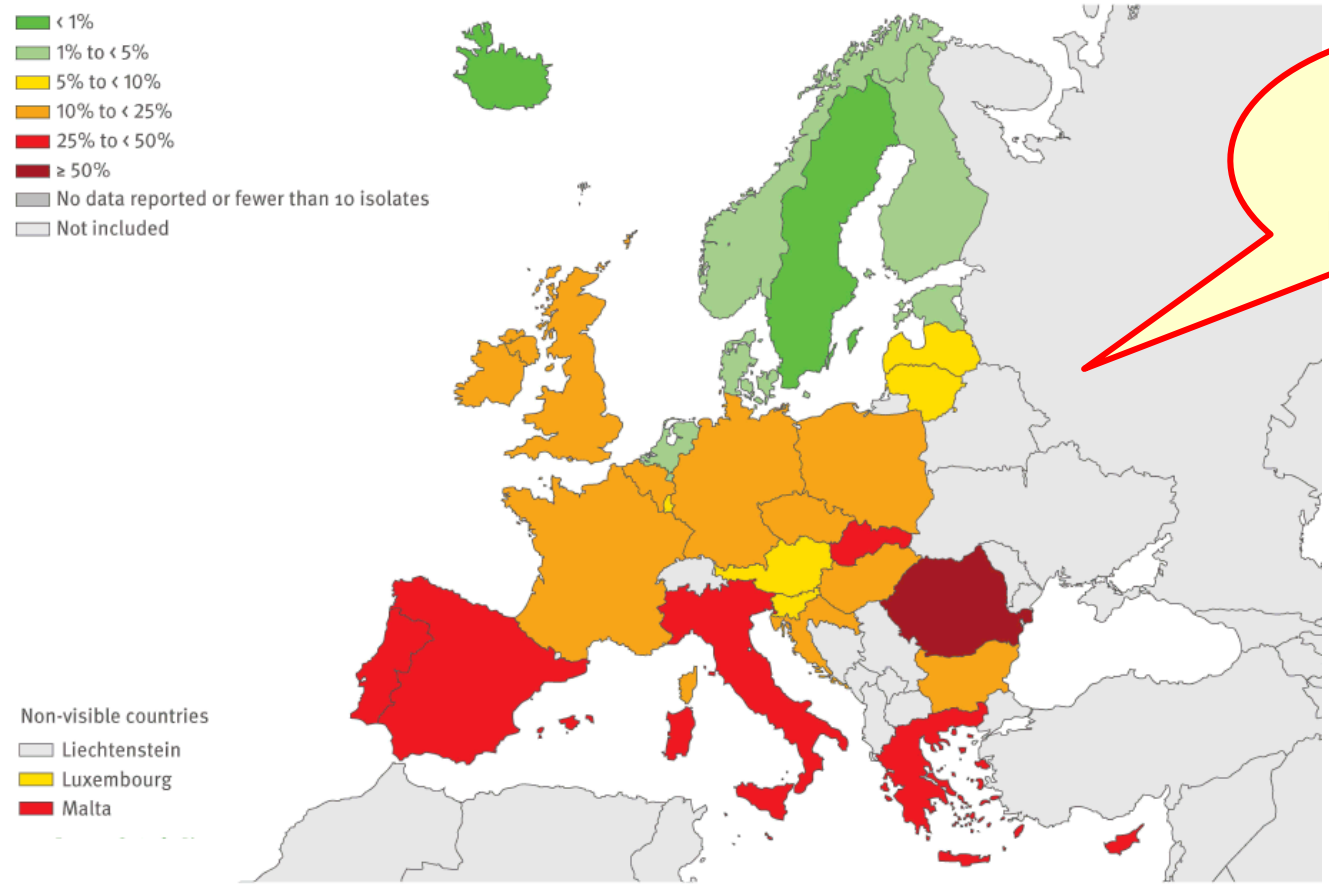
  - "*vancomycin, daptomycin, televancin, ceftaroline or linezolid should be used empirically in patients with severe soft tissue infections who are toxic or in those who have recently been hospitalized or received antibiotics.*"

  - "*But TMP–SMX or doxycycline are reasonable choices though choices should be guided by local antibiograms or cultures and sensitivities*."

[1] Clinical Features, Diagnosis and Management of Specific Soft Tissue Infections, In Infectious Diseases, Cohen, Powderly & Opal, eds, 4th edition, chapter 10, Elsevier, 2017 – available on line at https://expertconsult.inkling.com (last visited 9/04/2017)

Knowledge of local epidemiology is essential

Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2015



we all know these very useful maps…

Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Stockholm: ECDC, 2017
© European Centre for Disease Prevention ans Control, 2017

Antimicrobial resistance surveillance in Europe 2015 -
available on http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf (last visited: 9/4/2017)

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this was its first name… and colour… [1]

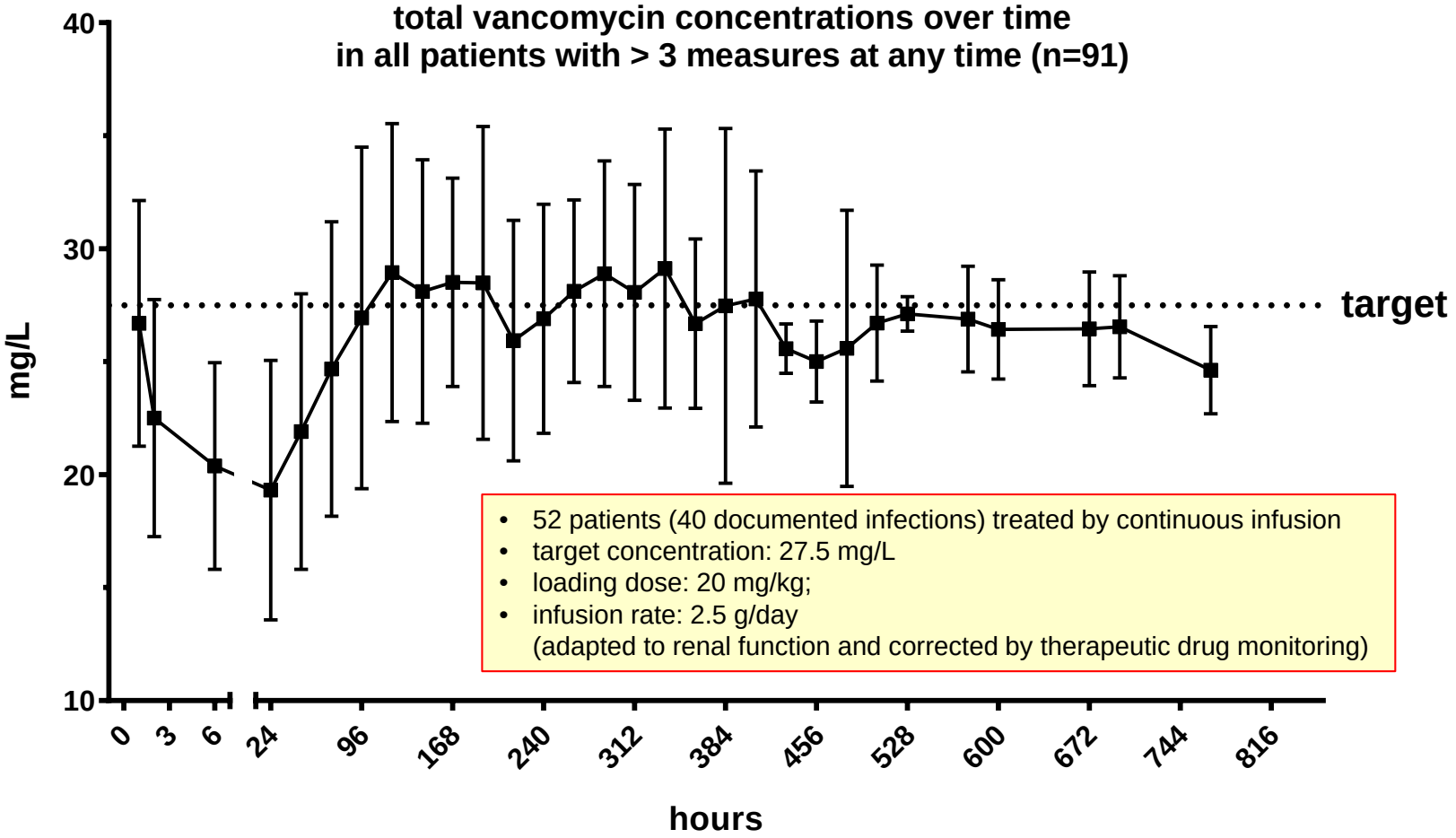
[1] Levine DP Clin Infect Dis. 2006;42 Suppl 1:S5-12 - PMID 16323120.

If we elect to use vancomycin …

- Beware of the presence of VISA [1] or hetero-VISA [2] strains AND look at MIC (should be ≤ 2 mg/L) [3]
- Use IV with slow infusion (1h) to avoid the "red man syndrome"
- Do not forget to monitor (even if using continuous infusion [4]) and to adjust dosages to cover the target organisms and obtain a sufficient AUC/MIC ratio (probably 400)
  → through level > 15 mg/L or for continuous infusion: 20-25 mg/L) [5]
  → correct for variable renal function (both ↘ and ↗ !)
- The standard treatment length is 10 days (on IV) (often 7-14 days) [4]
- Be prepared for nephrotoxicity in relation (i) to through levels > 15 mg/L[6] (or CI levels > 28 mg/L[7]), and (ii) length of treatment [2]

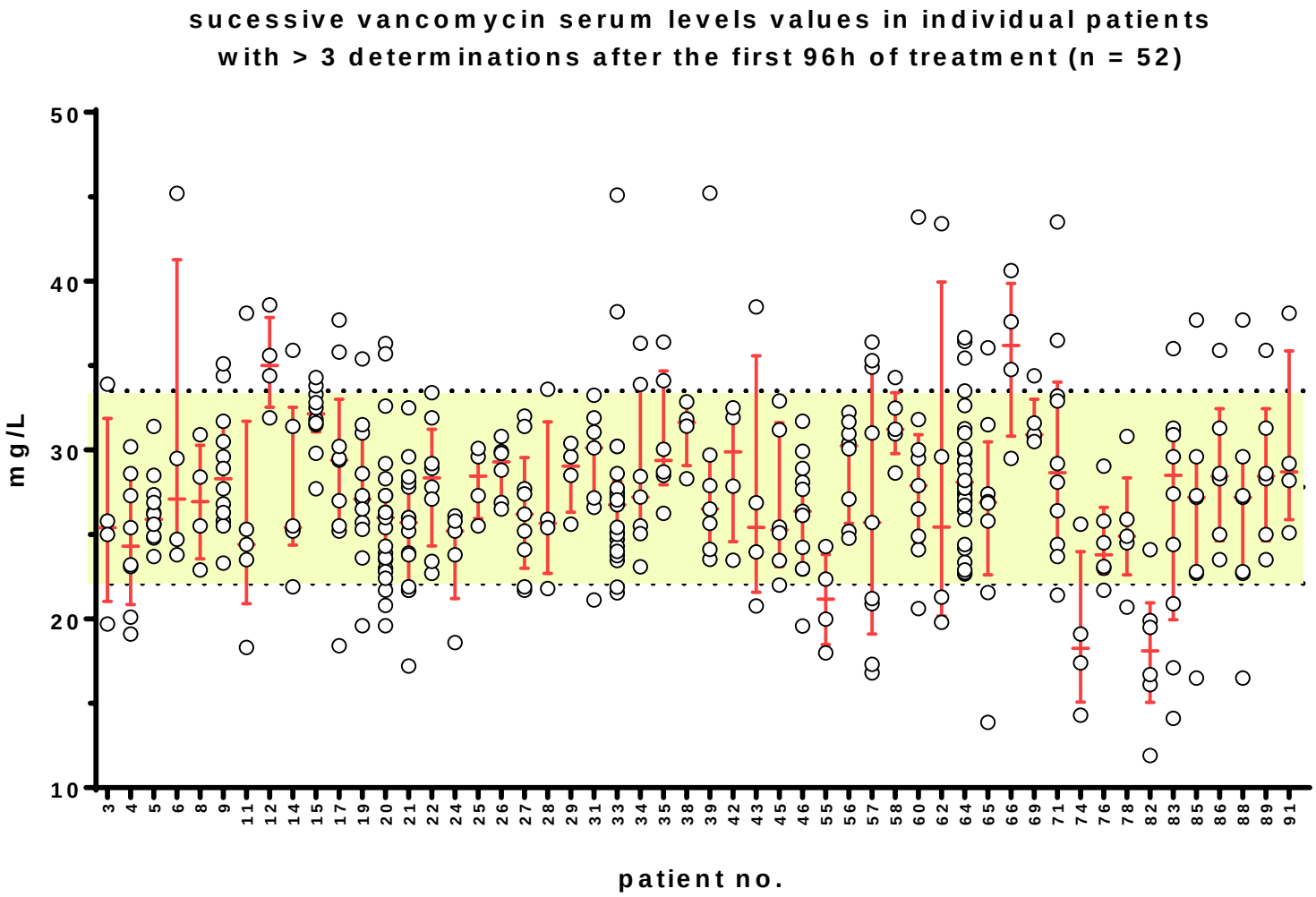
[1] VISA isolates also show an elevated MIC to daptomycin and may not be [fully] covered by dalbavancin and oritavancin
[2] Murray et al. Glycopeptides (Vancomycin and Teicoplanin), Streptogramins (Quinupristin-Dalfopristin), Lipopeptides (Daptomycin), and Lipoglycopeptides (Telavancin), In Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th edition, chapter 30, 2016 – available on line at https://expertconsult.inkling.com (last visited 9/04/2017)
[3] EUCAST "S" breakpoint (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf - last accessed: 09/04/2017)
[4] see next slides
[5] in bacteraemia, vancomycin failure has been associated with low initial vancomycin through levels (<15 µg/mL) and high vancomycin MIC (Etest: >1 µg/mL) (Kullar et al. Clin Infect Dis 2011;52:975-981 - PMID 21460309)
[6] Bosso et al. Antimicrob Agents Chemother 2011;55:5475-5479 - PMID 21947388
[7] Ingram et al. J Antimicrob Chemother. 2008;62:168-171 - PMID 18334494.

Vancomycin monitoring with continuous infusion: mean values look pretty nice…



Ampe *et al.*, Int J Antimicrob Agents 2013;41:439-446 – PMID 23523733

But individual and daily values are variable…



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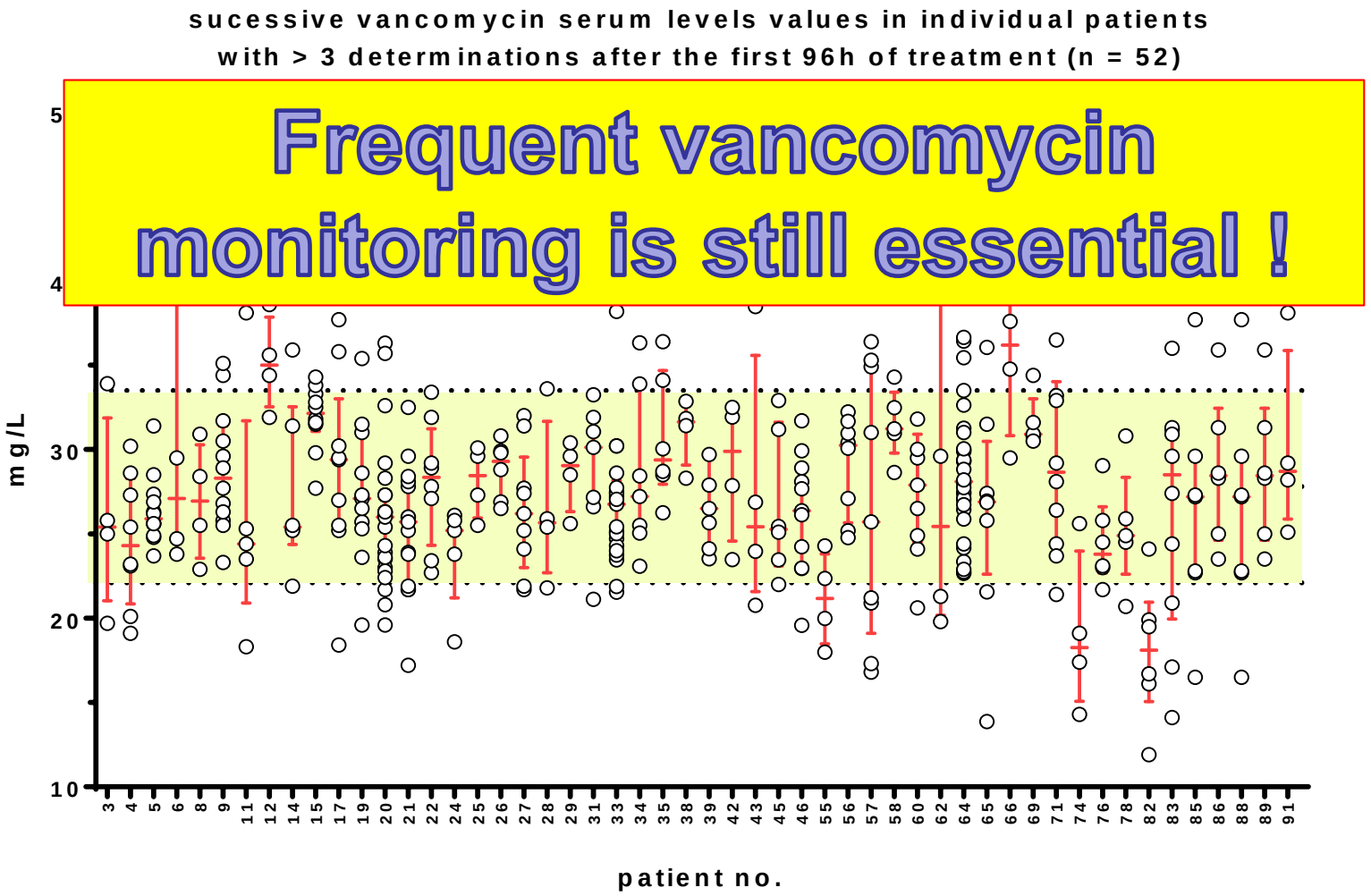

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which way do you want to go ?

Treatment duration…

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Matthew Dryden [a,*], Arjana Tambic Andrasevic [b], Matteo Bassetti [c], Emilio Bouza [d], Jean Chastre [e,f], Mo Baguneid [g], Silvano Esposito [h], Helen Giamarellou [i], Inge Gyssens [j,k,l], Dilip Nathwani [m], Serhat Unal [n], Andreas Voss [o], Mark Wilcox [p]

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3.3.2.6. In your opinion, what is the optimal duration of therapy for most patients with MRSA complicated skin and soft-tissue infections?

Responses. Most respondents (70%) believed that ⩾10 days was the optimum duration of therapy for patients with cSSTIs due to MRSA.

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Discussion points. These findings suggest that many patients are being treated for too long. Unnecessary usage of antibiotics is one of the key factors driving antibiotic resistance. For cSSTIs due to MRSA, current evidence and guidelines support a shorter period of treatment. Longer courses (10–14 days) should only be considered in patients with a slow clinical response.

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desired … but

MRSA infections: what do clinicians wish…

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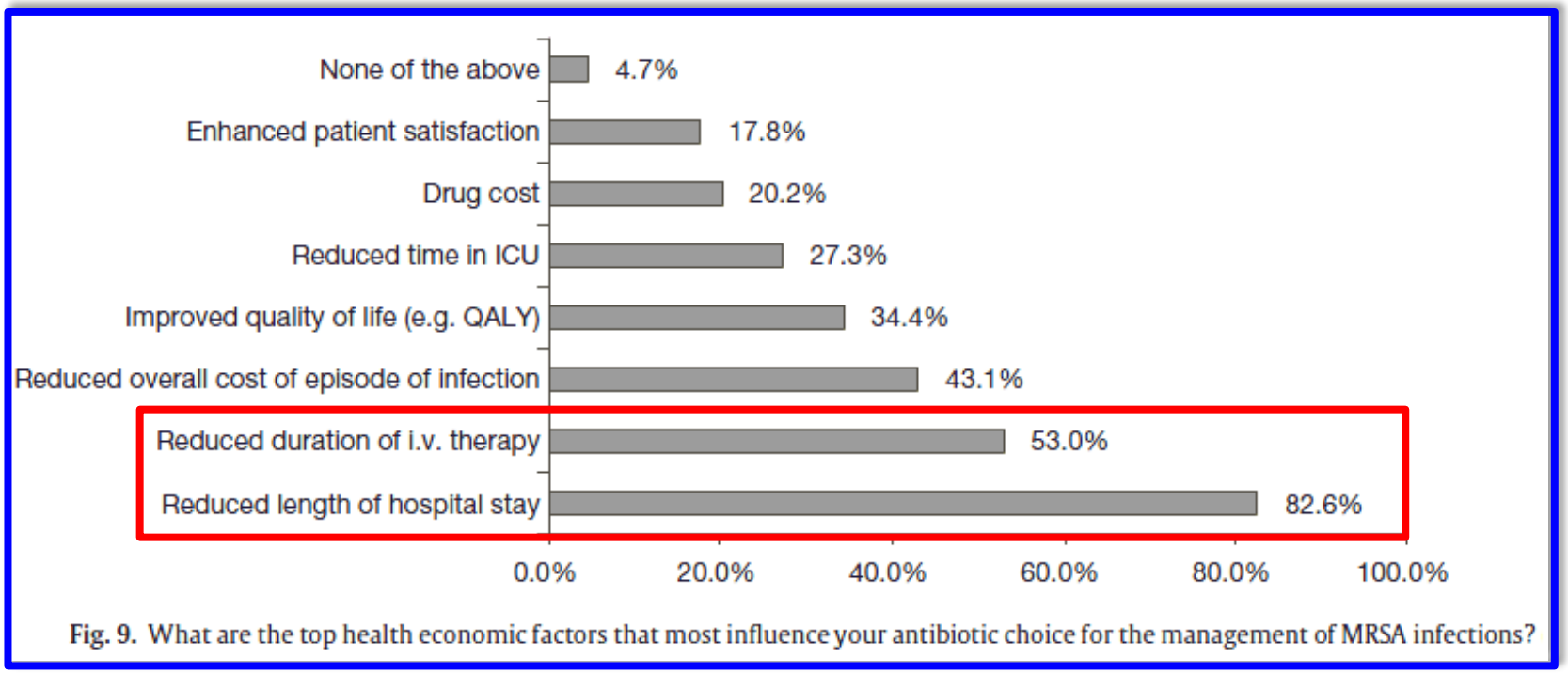

Fig. 9. What are the top health economic factors that most influence your antibiotic choice for the management of MRSA infections?

Dryden et al. Int J Antimicrob Agents. 2015;45 Suppl 1:S1-14 - PMID: 25867210.

Yet, here is what treatment duration is even if early switch/early discharge is possible

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International Journal of Antimicrobial Agents 44 (2014) 56–64

Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

Christian Eckmann[a], Wendy Lawson[b], Dilip Nathwani[c], Caitlyn T. Solem[d], Jennifer M. Stephens[d,*], Cynthia Macahilig[e], Damien Simoneau[f], Petr Hajek[g], Claudie Charbonneau[f], Richard Chambers[h], Jim Z. Li[i], Seema Haider[j]

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

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- **1502 patients with confirmed MRSA typical cSSTI** (cellulitis, abscess, wound or ulcer, …[requiring substantial surgical intervention]; exclud. diabetic foot, osteomyelitis, endocarditis, meningitis, joint infection, necrotising fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection…)
- **across 12 EU countries**
- **Early switch (ES) criteria:**
  - afebrile (< 38°C for 24h)
  - normalized WBC (not > 4 x 109 and not > 12 x 109 /L)
  - no unexplained tachycardia
  - SBP ≥ 100 mm Hg
  - oral fluids and medication tolerated
- **Early discharge (ED)**
  - all of the ES criteria
  - no reason to stay in hospital except infection treatment
- 1st line antibiotic: vancomycin (IV)
- Switch to oral: mainly with linezolid (main reason for ED)

Eckmann *et al.* Int J Antimicrob Agents 2014;44:5[illegible] PMID 24928511

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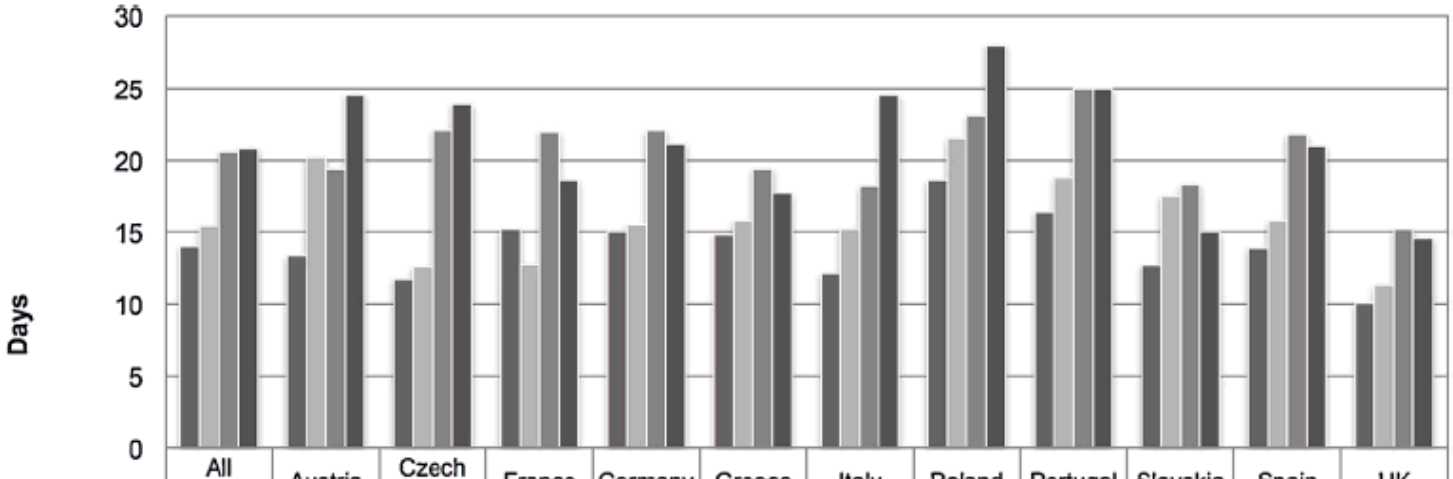

	All Countries (n=1502)	Austria (n=54)	Czech Republic (n=41)	France (n=261)	Germany (n=217)	Greece (n=151)	Italy (n=190)	Poland (n=43)	Portugal (n=141)	Slovakia (n=50)	Spain (n=183)	UK (n=169)
IV days- Full Cohort	14.0	13.4	11.7	15.2	15.0	14.8	12.1	18.6	16.4	12.7	13.9	10.1
IV days- ES Eligible Patients*	15.4	20.2	12.6	12.8	15.5	15.8	15.2	21.5	18.8	17.5	15.8	11.3
LOS- Full Cohort	20.6	19.4	22.1	22.0	22.1	19.4	18.2	23.1	25.0	18.3	21.8	15.2
LOS- ED Eligible Patients*	20.8	24.5	23.9	18.6	21.1	17.7	24.5	28.0	25.0	15.0	21.0	14.6

Fig. 1. Observed intravenous (i.v.) days and length of stay (LoS) from complicated skin and soft-tissue infection index date.
* The number of early switch (ES)- and early discharge (ED)-eligible patients is a subset of the sample sizes listed by country.

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

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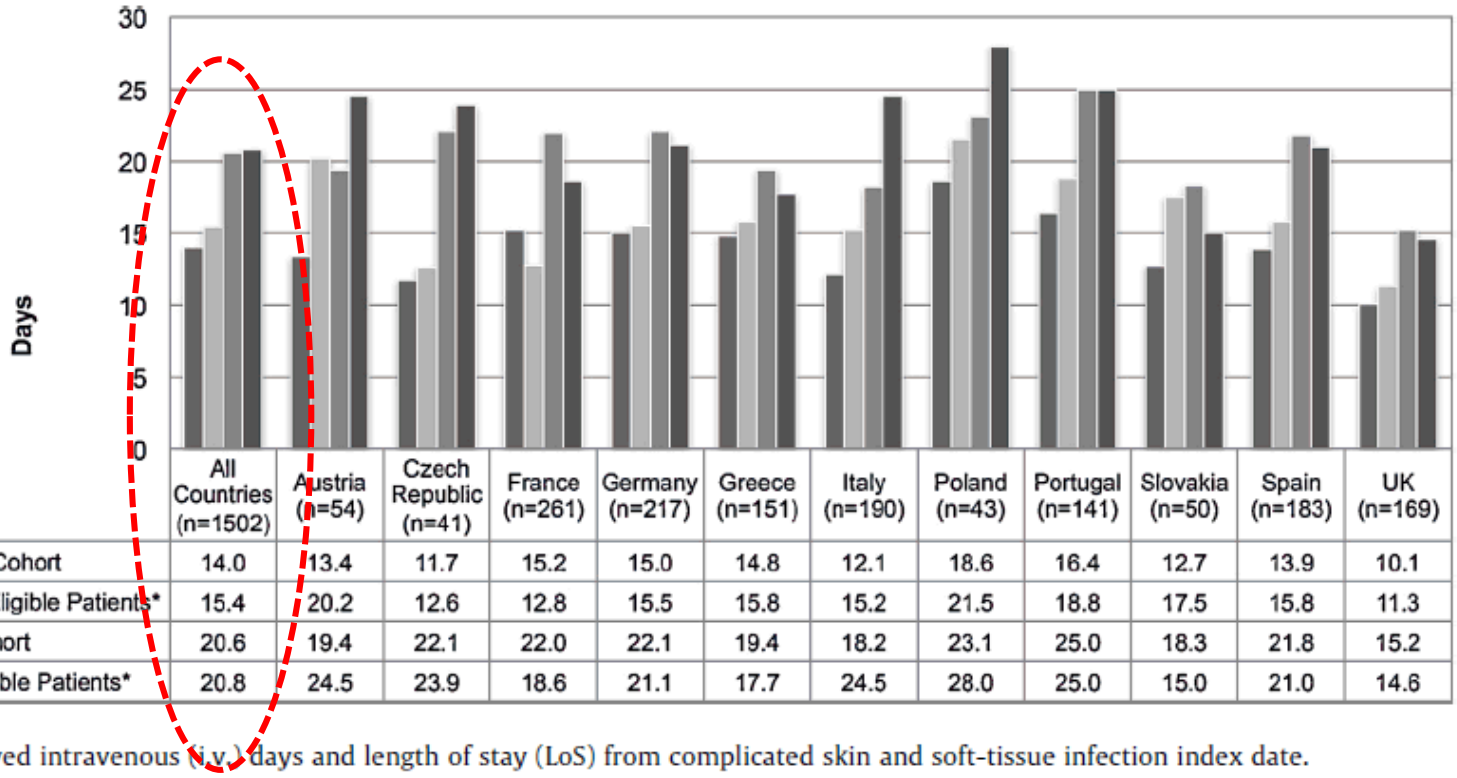

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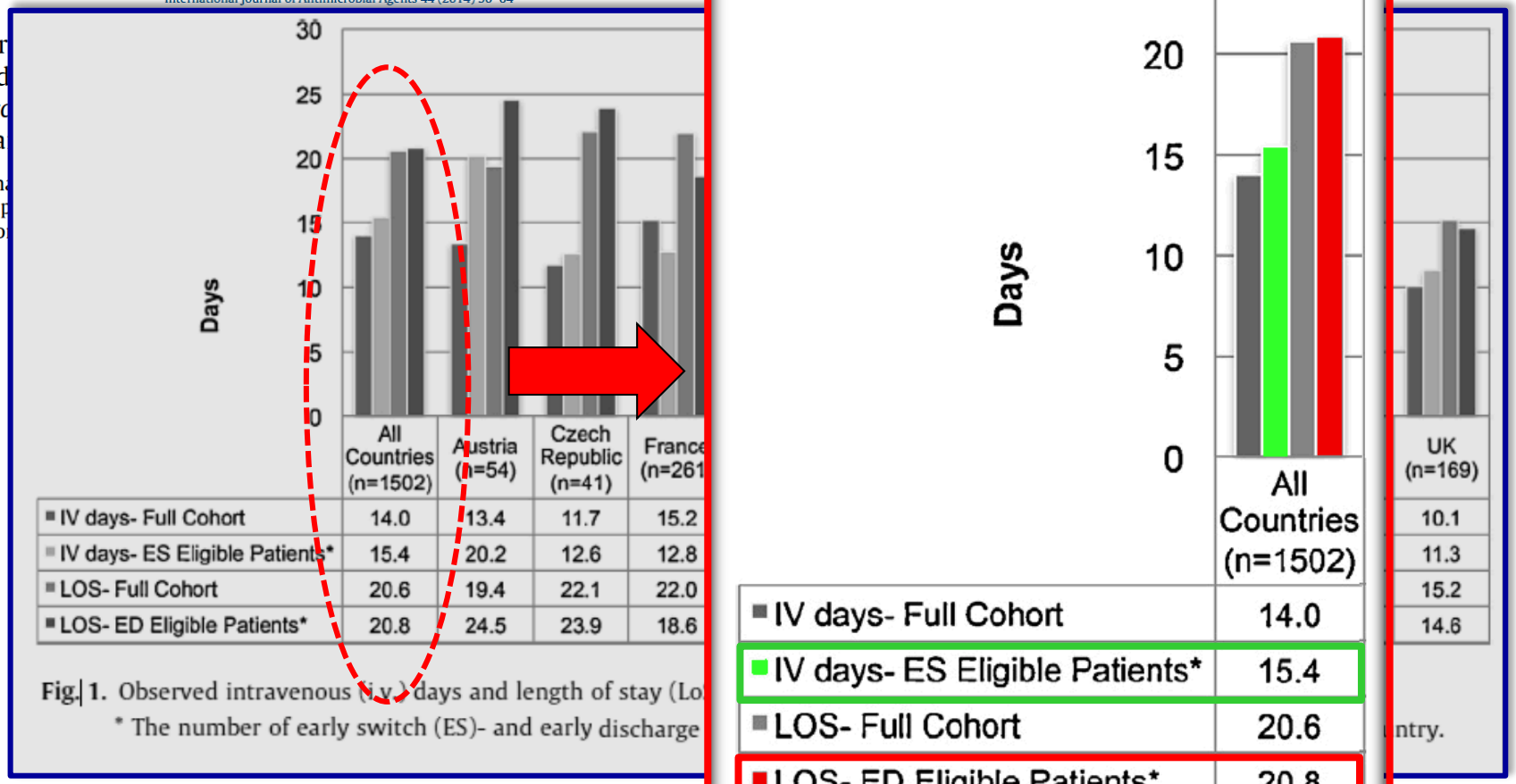

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Do we have criteria ? Back to future !

BMC Infectious Diseases

BioMed Central

Research article

Open Access

A new approach to treatment of resistant gram-positive infections: potential impact of targeted IV to oral switch on length of stay

Mohammed Desai[2], Bryony Dean Franklin[2,5], Alison H Holmes[1,4], Sarah Trust[2], Mike Richards[4], Ann Jacklin[2] and Kathleen B Bamford*[1,3]

Desai *et al.* BMC Infect Dis. 2006;6:94 - PMID 16762061

ORIGINAL ARTICLE

Implementing criteria-based early switch/early discharge programmes: a European perspective

D. Nathwani[1], W. Lawson[2], M. Dryden[3], J. Stephens[4], S. Corman[4], C. Solem[4], J. Li[5], C. Charbonneau[6], N. Baillon-Plot[6], S. Haider[7] and C. Eckmann[8]

1) Ninewells Hospital and Medical School, Dundee, 2) Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, 3) Hampshire Hospitals NHS Foundation Trust, Winchester, Hampshire, UK, 4) Pharmerit International, Bethesda, MD, 5) Pfizer Inc., San Diego, CA, USA, 6) Pfizer Inc., Paris, France, 7) Pfizer Inc., Groton, CT, USA and 8) Klinikum Peine, Academic Hospital of Medical University Hannover, Peine, Germany

Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

Criteria for Early Switch / Early Discharge

BMC Infectious Diseases

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Research artic
A new appr
potential ir
Mohammed
Sarah Trust[2],

Desai *et al.* BMC I

Table 1: IV to oral switch inclusion criteria used

1. Clinical status	• Temperature less than 38°C for 24 hours • White cell count normalising • No unexplained tachycardia (Heart rate less than 100 beats per minute) • Sensitivity received (if microbiology positive)
2. Oral absorption	• Patient tolerates oral fluids • No medical problems leading to reduced oral absorption (e. g. vomiting, diarrhoea, and gastrointestinal surgery) • No surgical operation scheduled within next 36 hours

Table 2: IV to oral switch exclusion criteria used

1. Continuing sepsis	• Temperature less than 36°C or more than 38°C • White cell count less than 4 × 10^9/L or more than 12 × 10^9/L • Unexplained tachycardia (Heart rate greater than 100 beats per minute in last 12 hours)
2. Oral route compromised	• Vomiting or severe diarrhoea • Other ongoing or potential absorption problem

Criteria for Early Switch / Early discharge

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S. Haider[7] and C. Eck
1) *Ninewells Hospital and*
Foundation Trust, Winchest
Inc., Groton, CT, USA and

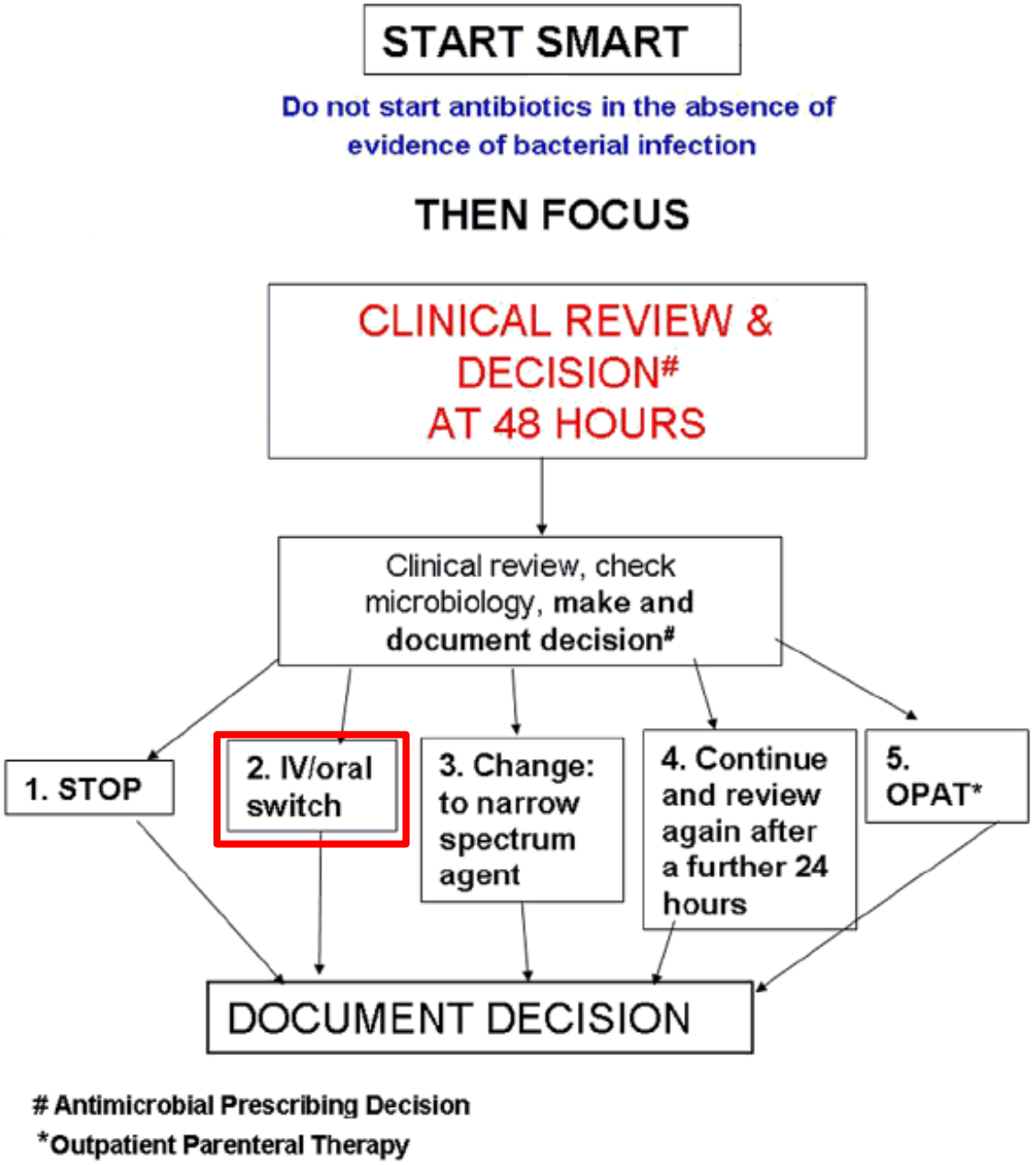
Nathwani *et al*. Clin

TABLE 1. Criteria used to determine patient eligibility for intravenous to oral antimicrobial switch therapy

Criteria
Temperature <38°C or >36°C for 24–48 h; normalizing body temperature; afebrile for at least 8–24 h [5,9,12,14,16–18,20,21,23,25]
No unexplained tachycardia, haemodynamic instability [7,9,14,16,21,23,25]
Clinical improvement, no clinical indication for intravenous therapy [5,7,9,12,17–20,23,25]
Oral fluids/food tolerated, no reason to believe oral absorption of antimicrobials may be poor; may be by nasogastric/gastric feeding tube [5,7,9,12,14–20,22,23,25]
Improving white blood cell count [5,9,12,14,16,17,20,23,25]
Improving C-reactive protein [5,9]
Suitable oral antimicrobial therapy [9,12,23,24,33]
No surgery scheduled within next 24–36 h [16,25]

Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

Early Switch should be part of a policy



Adapted from:

- Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369
- Antimicrobial stewardship: "Start smart – then focus"; guidance for antimicrobial stewardship in hospitals (England).2011; available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215308/dh_131181.pdf (last visited: 9/04/2017)

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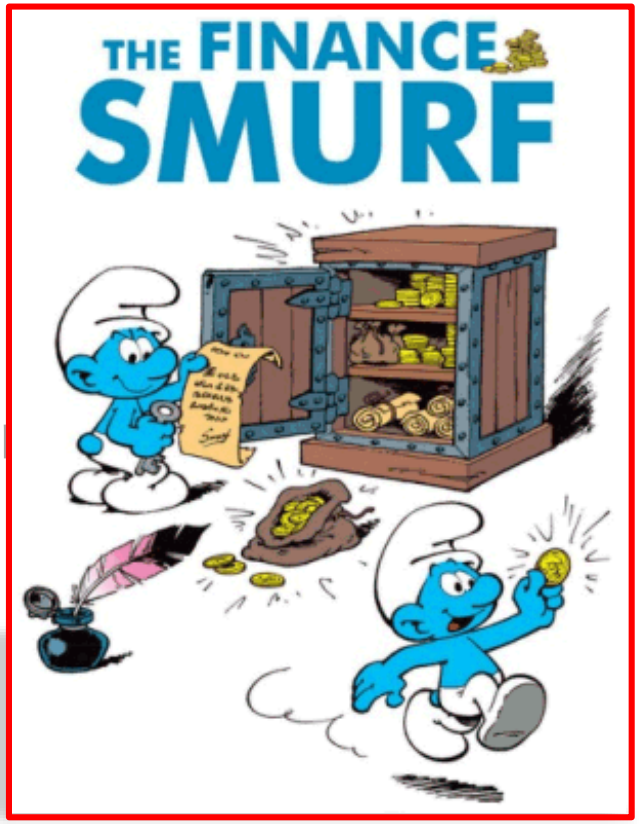
- Do we have criteria ?
- **What do we save ?**
- Sum up … and questions, suggestions, objections …



What can you save ?

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

International Journal of Antimicrobial Agents 44 (2014) 56–64

Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant *Staphylococcus aureus*: A plea for implementation of early switch and early discharge criteria

Christian Eckmann[a], Wendy Lawson[b], Dilip Nathwani[c], Caitlyn T. Solem[d], Jennifer M. Stephens[d,*], Cynthia Macahilig[e], Damien Simoneau[f], Petr Hajek[g], Claudie Charbonneau[f], Richard Chambers[h], Jim Z. Li[i], Seema Haider[j]

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

Yet, here is what treatment duration is even if early switch/early discharge is possible

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International Journal of Antimicrobial Agents 44 (2014) 56–64

Antibi
compl
Staphy
early

Christia
Jennifer
Claudie

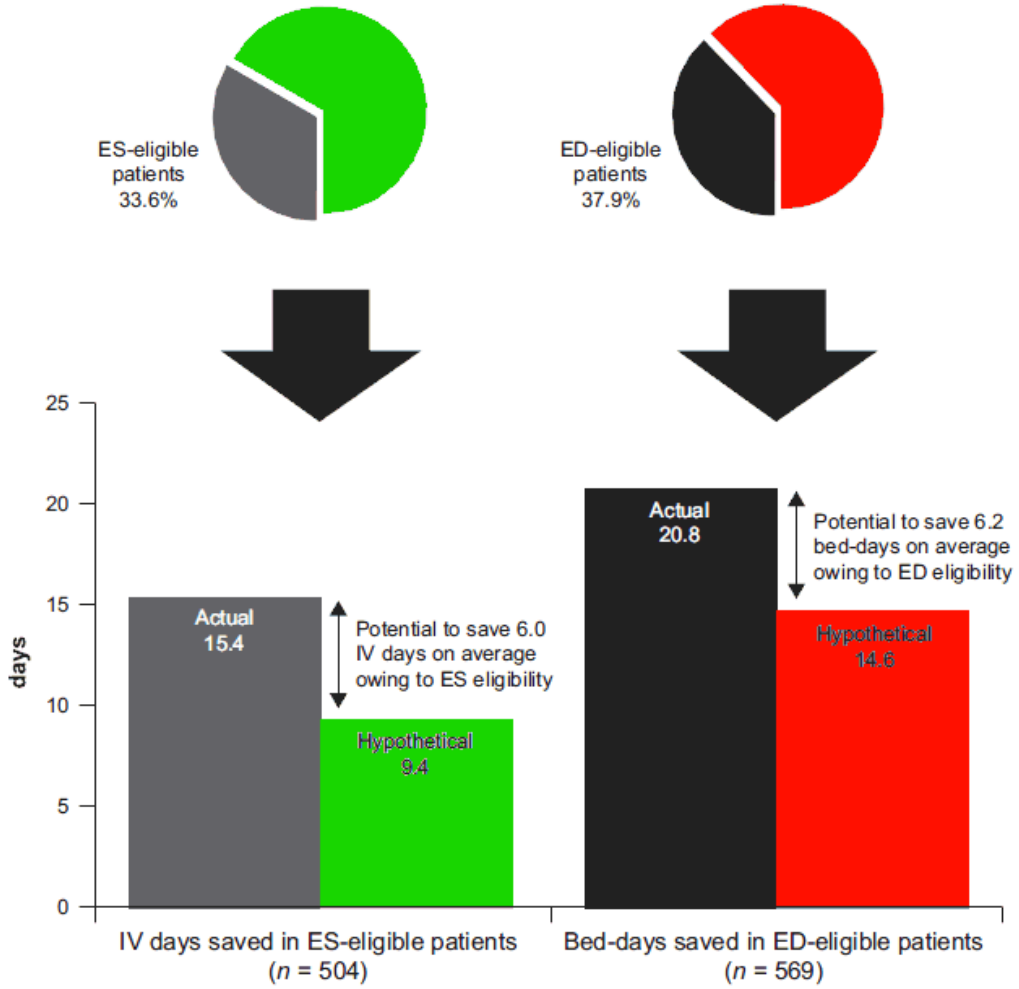
Early switch (ES) and early discharge (ED) eligibility and potential savings in intravenous (i.v.) days, hospital length of stay and costs.

			Potential cost savings due to bed-days saved	
	ES-eligible (%)	ED-eligible (%)	Average cost (€344.87 per bed-day)[a]	Country-specific costs (2012€)[a,b]
All countries (n = 1502)[c]	33.6	37.9	2135 ± 2829	2129 ± 2846
Austria (n = 54)	25.9	33.3	2088 ± 2023	2716 ± 2631
Czech Republic (n = 41)	22.0	46.3	1833 ± 2247	1495 ± 1832
France (n = 261)	28.4	35.2	2703 ± 3643	2864 ± 3861
Germany (n = 217)	46.5	47.0	1454 ± 1912	1683 ± 2214
Greece (n = 151)	56.3	41.1	2581 ± 3644	2317 ± 3272
Italy (n = 190)	25.3	34.2	2430 ± 2785	2642 ± 3028
Poland (n = 43)	32.6	27.9	2270 ± 2203	1235 ± 1199
Portugal (n = 141)	42.6	48.2	2216 ± 2445	1592 ± 1756
Slovakia (n = 50)	12.0	10.0	414 ± 154	320 ± 119
Spain (n = 183)	26.2	38.8	2327 ± 3136	2193 ± 2955
UK (n = 169)	26.6	32.5	1499 ± 2024	1872 ± 2528

Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID 24928311

Hypothetical gain values ?

FIG 1. Comparison of actual and hypothetical intravenous (IV) days and bed-days in early switch (ES)-eligible and early discharge (ED)-eligible patients.



Nathwani *et al*. Clin Microbiol Infect 2015;21 Suppl 2:S47-55 -PMID 26198369

A little bit of pharmacoeconomy …

- **Direct costs:**
  - all **directly consumed resources** by the use of the medication
    - Medical costs: drug acquisition, administration, diagnostic and surveillance tests, consultation(s), prevention and treatment of adverse effects, hospitalisation …
    - Non medical costs: transport(s), family help …
- **Indirected costs:**
  - all **costs associated to the change in productivity** related to the drug
    - time needed for the treatment (patient, family, helpers, …)
    - inability to work or to produce goods important for daily life
    - Death (causing an economic loss)…
    - Costs related to the foreseeable future

Adapted from L. Sanchez Trask Pharmacoeconomics: Principles, Methods, and Applications . In Pharmacotherapy: a pathophysiologic approach, J.T. Di Piro et al eds., 8th ed. Appelton & Lange - http://accesspharmacy.mhmedical.com/book.aspx?bookid=462 (last accessed: 09/042017)

Examples of costs

vancomycin is cheap…

Category	Costs
Direct medical costs	Drug acquisition costs Other objects needed for drug use Laboratory tests to perform Staff working time Hospitalization (duration and ward)
Direct non-medical costs	Transport of the patient Needs of the patient (home or hospital) Care of family Home helpers
Indirect costs	Losses related to the disease (morbidity) Losses related to death (mortality)
Intangible costs	Pain Isolation from family Grief
Opportunity costs	Lack of opportunities (due to hospitalization) Irreversible economic losses

but do not forget to include this…

Adapted from L. Sanchez Trask Pharmacoeconomics: Principles, Methods, and Applications . In Pharmacotherapy: a pathophysiologic approach, J.T. Di Piro et al eds., 8th ed. Appelton & Lange - http://accesspharmacy.mhmedical.com/book.aspx?bookid=462 (last accessed: 09/042017)

Novel anti-MRSA approved in Europe*…

class	drug	cSSTI / ABSSSI **	
		administration	treatment duration
β-lactams	ceftaroline	IV – 60 min Q12h [1]	5-14 days
	ceftobiprole [2]	--	--
oxazolidinones	tedizolid	IV or oral – 200 mg QD	6 days
lipoglycopeptides	telavancin [3]	--	--
	dalbavancin	1.5 g IV once or 1 g IV + 500 mg at day 7	1 or 7 days
	oritavancin	1.2 g over 3 h once	1

***** based on EMA Summary of Product Characteristics for ZINFORO®, SIVEXTRO®, VIBATIV®, XYDALBA®, and ORBACTIV® (http://www.ema.europa.eu last accessed: 9/04/2017)

** cSSTI: complicated skin and soft tissue infections / ABSSSI: acute bacterial skin and skin structure infections (see definitions and explanation for different denominations in Pollack *et al.* J Emerg Med 2015;48:508-519 - PMID 25605319)

[1] every 8h with 2h infusion for MRSA for which MIC is 2 or 4 mg/L

[2] not approved in EU (approved [decentralized procedure] for CAP and HAP [excluding VAP]; see UK Summary of Product Characteristics [last accessed: 9/04/2017])

[3] not approved for cSSTI in EU but approved in the US - approved or MRSA nosocomial pneumonia [including VAP]

So, what is really new over the good old vancomycin *…

Drug	advantages **	risks **
ceftaroline	• no need of monitoring • ↘ risk of nephrotoxicity [1]	• allergic reactions • **MRSA MICs ↗**
tedizolid	• **6 days treatment** (< LZD) • active against cfr+ LZR^{R} • **easy oral switch** (= LZD but QD) • **no monitoring and no dosage adjustment needed**	• neutropenic patients • safety not established for treatments > 6 days
dalbavancin oritavancin	• **single injection** [2] • **no monitoring** (not applicable) and **no need of dosage adjustment** [3]	• perturbation of coagulation and liver laboratory tests • uncertain activity against **VISA strains** • very long tissue residence

* assuming the isolate is susceptible to vancomycin (MIC ≤ 2 mg/L – EUCAST breakpoint (see http://www.eucast.org)

** personal selection based on analysis of the respective EMA Summary of Product Characteristics (http://www.ema.europa.eu - last accessed: 9/04/2017) see also Table 1 in Pollack *et al.* J Emerg Med 2015;48:508-519 - PMID 25605319 for more detailed pros and cons for Emergency Physicians and Hospitalists)

[1] compared to vancomycin (but preclinical studies show early renal toxicity in monkeys and rats – see EMA Summary of Product Characteristics for ZINFORO®)

[2] a second injection after one week may be needed for dalbavancin (see EMA Summary of Product Characteristics for XYDALBA®)

[3] pharmacokinetics in patients with severe renal and hepatic impairment have not been investigated (see EMA Summary of Product Characteristics for ORBACTIV®)

The programme…

- Novel therapies …
- Old (good) vancomycin ?
- Treatment duration …
- Early switch / Early discharge is possible…
- Do we have criteria ?
- What do we save ?
- **Sum up … and questions, suggestions, objections …**

To sum up…

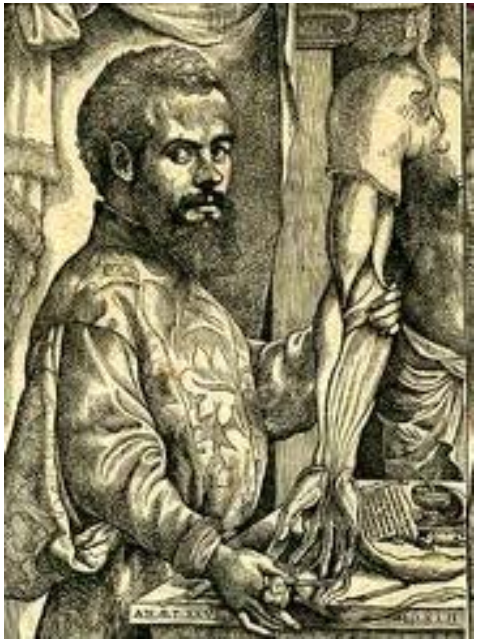
- There is now good evidence that Early Switch (ES) and Early Discharge are possible for cSSTI and can be implemented based on solid and objective criteria…

- ES and ED may provide several advantages
  - epidemiological
  - pharmacoeconomics
  - quality of life

- New available anti-Gram positive drugs may provide the necessary background and help
  - "once IV dosing" (oritavancin/dalbavancin)
  - short course treatment with easy IV/oral switch (tedizolid)

We may move on now !

Please, ask questions …



be critical,
ask for facts !

Vesalius - anatomy

All slide are available on http://www.facm.ucl.ac.be → Lectures