Vancomycin-resistant enterococcus: how serious is the problem?

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Disclosures

- Education and research grants from Abbott, AstraZeneca, Gilead, Janssen, MSD, Novartis, Pfizer, Roche

Enterococci

- Gram positive cocci, part of the normal gut flora, with relatively low virulence
- Able to survive under harsh environmental conditions
- Capable of colonizing and persisting on environmental surfaces (including medical equipment) for prolonged periods
- Responsible for a variety of infections (endocarditis, bacteremia, UTI, meningitis, surgical wound infection…)
- Species of clinical significance mainly E. faecalis, E. faecium

Arias CA & Murray BE Expert Rev Anti Infect Ther 2008

Enterococcus: Antimicrobial Resistance

Intrinsic

- Antistaphylococcal penicillins
- Cephalosporins
- Clindamycin (low level)
- Co - trimoxazole
- Aminoglycosides (low level)
- Carbapenems (E. faecium)

Acquired

- Aminoglycosides (high level)
- Clindamycin (high level)
- Chloramphenicol
- Erythromycin
- Penicillin
- Tetracycline

McManus MC. Am J Health-Syst Pharm. 1997
Moellering RC Jr et al. Clin Infect Dis. 1992
Murray BE. Clin Microbiol Rev. 1990

Standard Regimen for Serious Enterococcal Infections

An agent acting on cell wall synthesis
(a β-lactam or a glycopeptide)
PLUS
an aminoglycoside

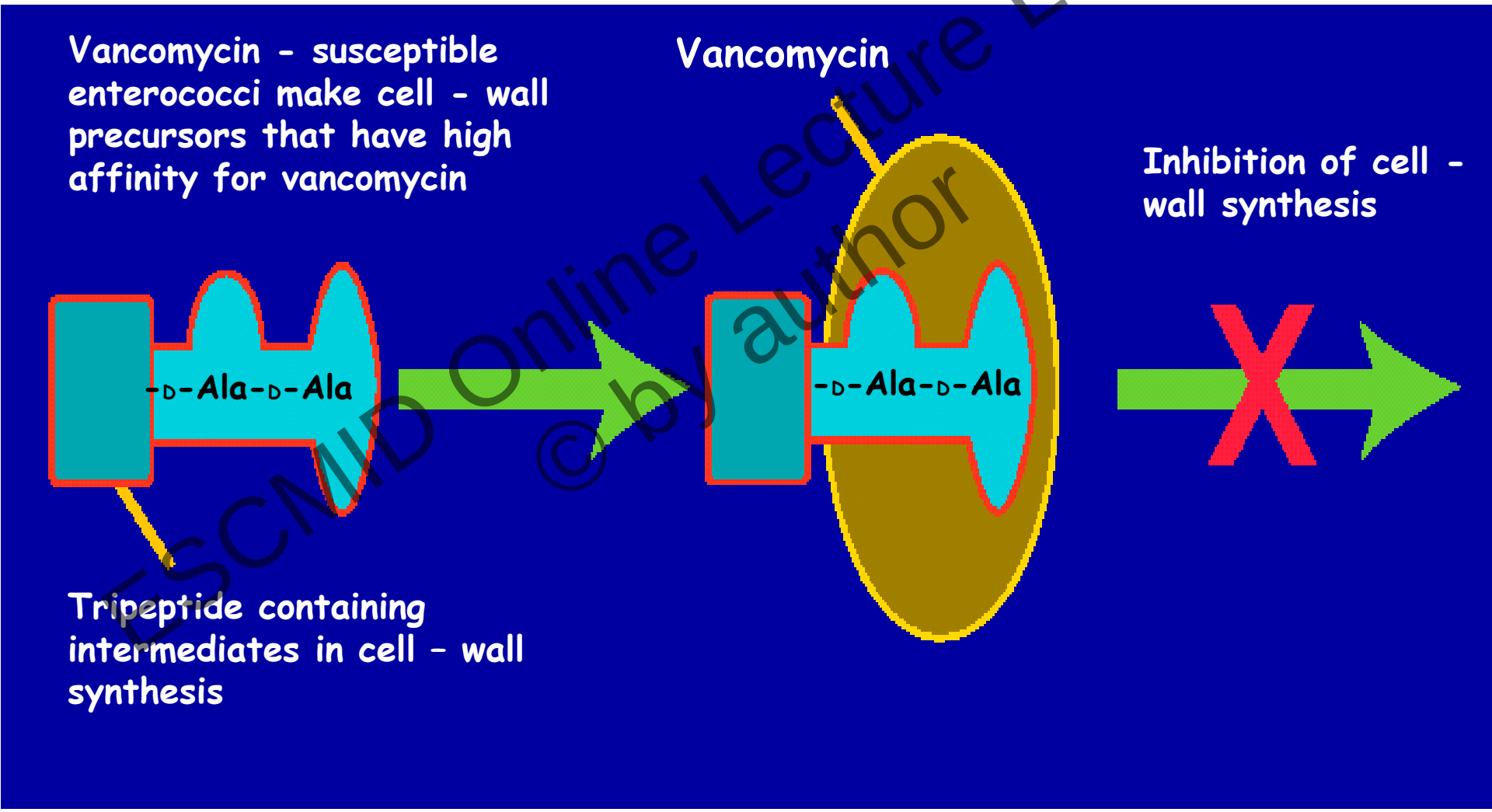
Murray BE. Clin Microbiol Rev. 1990

Vancomycin - Resistant Enterococcus (VRE)

- First time isolated in Europe (1986), then in USA (1989)
- In Europe role of avoparcin as growth promoter in animals
- In USA related to the massive increase of vancomycin use, due to MRSA and C. difficile (per os)

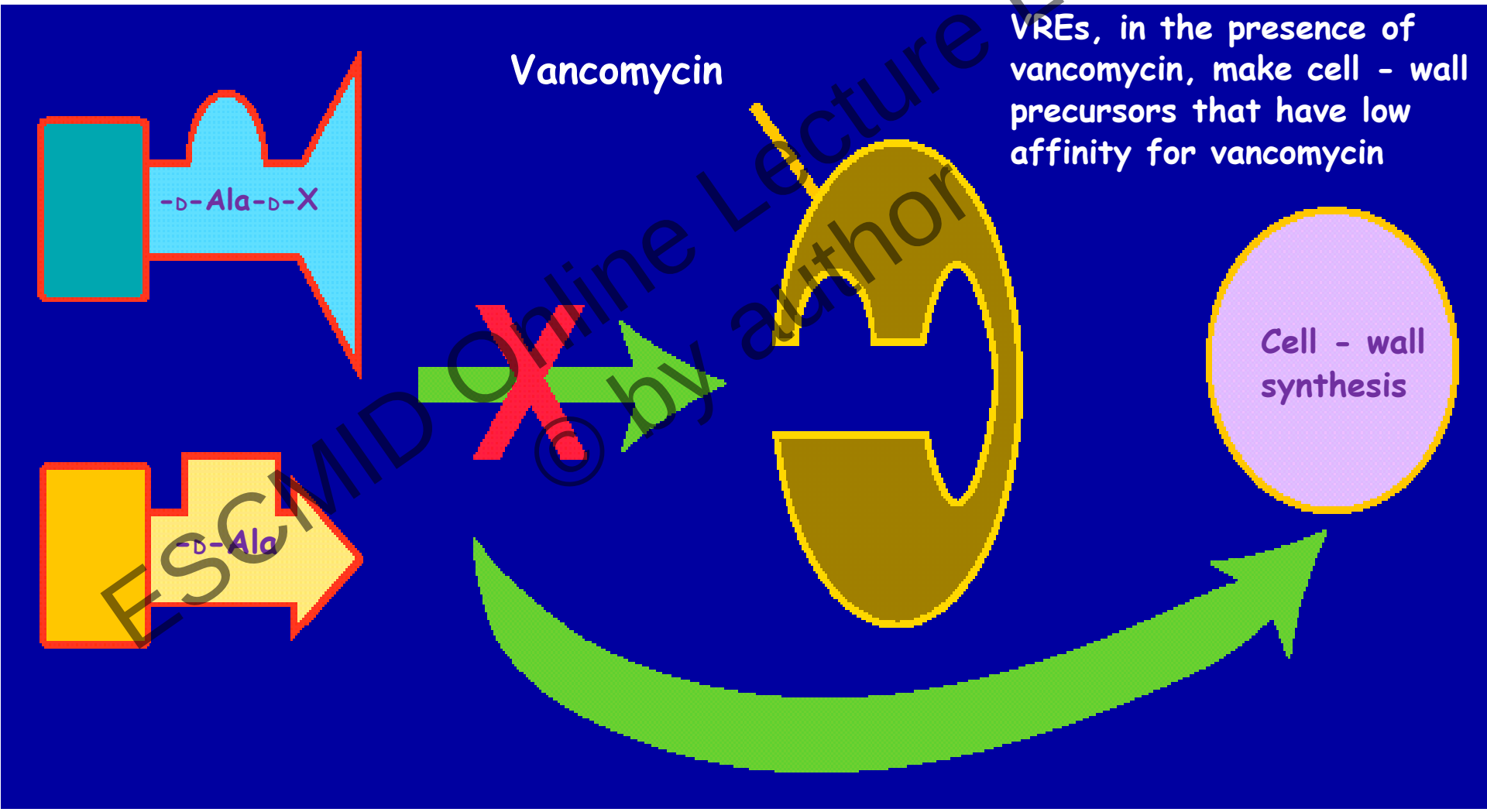
Cattoir V & Leclercq R, J Antimicrob Chemother 2013
LeClercq R et al, N Engl J Med 1988
Uttley A et al, Lancet 1988

Vancomycin - Susceptible Enterococci



Murray BE, *N Engl J Med* 2000

Vancomycin - Resistant Enterococci



Murray BE, *N Engl J Med* 2000

VRE : Resistance phenotypes ("The Van Alphabet")

Table 1. Characteristics of different types of vancomycin resistance described among *Enterococcus* spp

			Range of MIC (mg/L)				
	Sort	Modified target	Vancomycin	Teicoplanin	Expression	Location	Transferable
* vanA	Acquired	D-Ala-D-Lac	64–1000	16–512	Inducible	Chromosome or plasmid	Yes
vanB	Acquired	D-Ala-D-Lac	4–1000	0.5–1	Inducible	Chromosome or plasmid	Yes
vanC	Intrinsic	D-Ala-D-Ser	2–32	0.5–1	Constitutive or inducible	Chromosome	No
vanD	Acquired	D-Ala-D-Lac	64–128	4–64	Constitutive or inducible	Chromosome	No
vanE	Acquired	D-Ala-D-Ser	(6) 8–32	0.5	Inducible	Chromosome	No
vanG	Acquired	D-Ala-D-Ser	16	0.5	Inducible	Chromosome	Yes
vanL	Acquired	D-Ala-D-Ser	8	<8	Inducible	Chromosome	No
vanM	Unknown	D-Ala-D-Lac	>128	64 to >256	Inducible	Unknown	Yes
vanN	Acquired	D-Ala-D-Ser	16	0.5	Constitutive	Plasmid	Yes

MIC, minimum inhibitory concentration (mg/L).
D-Ala-D-Lac = D-Alanyl-D-Lactate, D-Ala-D-Ser = D-Alanyl-D-Serine.

* VanA the most prevalent worldwide, with some exceptions (Australia, Sweden)

Nilsson O, Infect Ecology & Epidemiol 2012

VRE's Success Story

- From a colonizer and second - rate pathogen, to one of the leading causes of hospital-acquired infections and a first - rate clinical problem!!!
- Reports from all over the world, endemic in some regions
- Rates of vancomycin – resistance up to 28% among enterococci
- E. faecium up to 93% (USA) and 74,1% (Europe) of VREs
- Increasing E. faecium percentage among enterococci (up to 20%-36%), attributed to the emergence of a specific genetic lineage (Clonal Cluster 17, CC - 17)

Arias CA et al, Clin Microbiol Infect 2010
Cattoir V & Leclercq R, J Antimicrob Chemother 2013
Deshpande LM et al, Diagn Microbiol Infect Dis 2007

VRE: A Worldwide Issue

Table 2. Frequency of resistance to vancomycin in enterococci isolated in various continents (adapted from reference 39)

	Percentage resistance to vancomycin according to region (no. of isolates)				
Species	Asia/Pacific	Europe	Latin America	North America	overall
E. faecium	14.1 (270)	31.5 (489)	48.1 (54)	76 (597)	47.6 (1410)
E. faecalis	0.01 (440)	1.5 (919)	3 (195)	5.6 (945)	3 (2499)
All	11.9 (710)	11.9 (1408)	12.9 (249)	32.8 (1542)	19.1 (3909)

Cattoir V & Leclercq R, J Antimicrob Chemother 2013

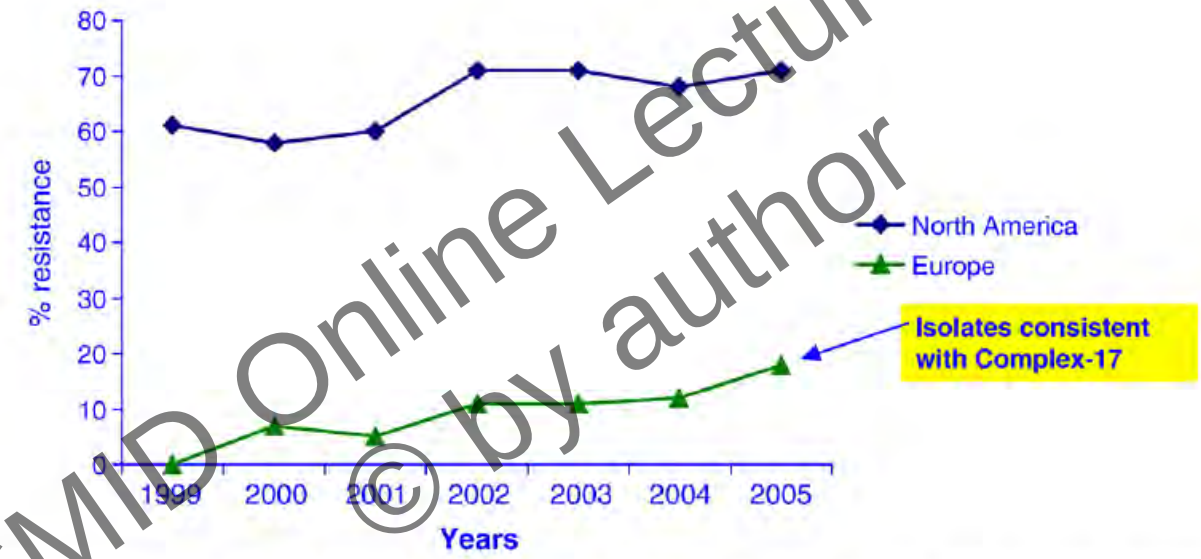


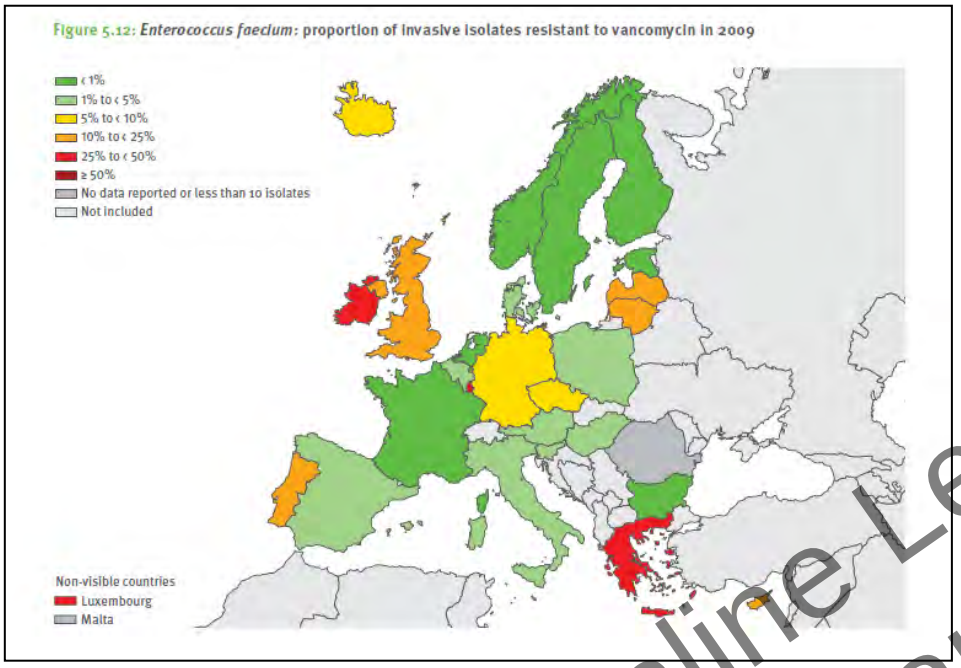
Fig. 2. Progression of vancomycin resistance in *E. faecium* among bloodstream isolates studied in North America and Europe, including presence of isolates with antibiograms consistent with those of CC-17 (SENTRY Program, 1999–2005).

Deshpande LM et al, Diagn Microbiol Infect Dis 2007

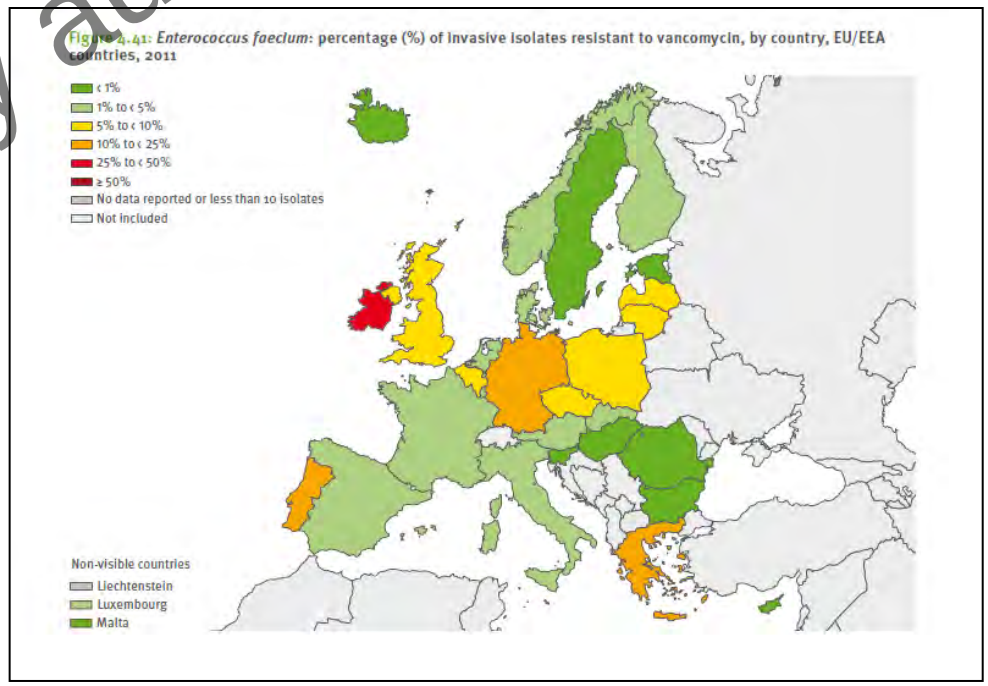
TABLE. Incidences of Adult Hospitalization With Infection Due to Vancomycin-Resistant *Enterococcus* (VRE) in the United States, by Age Group

Incidence, age group	Year						
	2000	2001	2002	2003	2004	2005	2006
No. of hospitalizations with VRE infection per 100,000 population							
18–44 years	0.95	1.17	1.57	1.24	1.48	1.93	2.47
45–64 years	3.83	3.70	3.80	3.52	4.48	6.12	7.66
65–84 years	15.54	16.34	15.67	14.63	17.02	23.18	29.47
⩾85 years	36.79	38.69	29.54	34.27	39.84	55.61	64.42
All	4.68	4.92	4.89	4.60	5.51	7.54	9.48
No. of hospitalizations with VRE infection per 10,000 hospitalizations							
18–44 years	1.08	1.34	1.75	1.40	1.62	2.17	2.74
45–64 years	3.23	3.11	3.15	2.89	3.70	5.15	6.29
65–84 years	4.71	4.77	4.64	4.36	5.17	7.03	8.96
⩾85 years	6.13	6.27	4.97	5.87	7.12	9.61	11.47
All	3.27	3.39	3.35	3.16	3.80	5.24	6.51

Ramsey AM & Zilberberg MD, Infect Control Hosp Epidemiol 2009

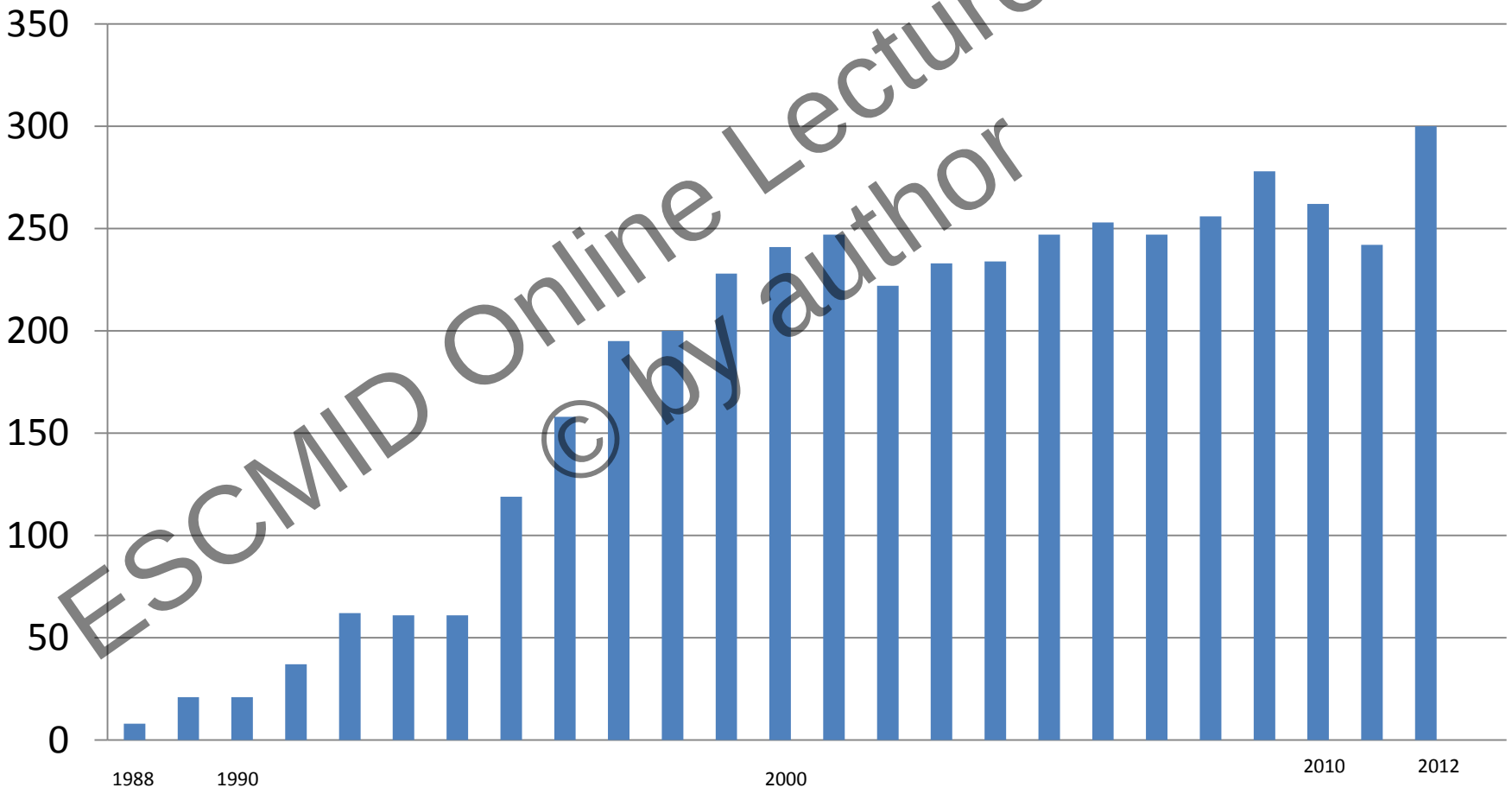


EARSnet 2009



EARSnet 2011

Results of pubmed search for "vancomycin resistant enterococcus"



VRE: The Nature of the Problem

- Infections are just the tip of the iceberg!!!
- It is crucial to differentiate infection from colonization!!!
- Colonization: Isolation from
  - Superficial wounds

No treatment for colonization!!!

  - Non pyuric urine
  - Biliary or intraperitoneal drains
- Infection: Isolation in two or more blood cultures or from normally sterile sites, with concomitant local or systemic signs of inflammation

Linden PK, Drugs 2002

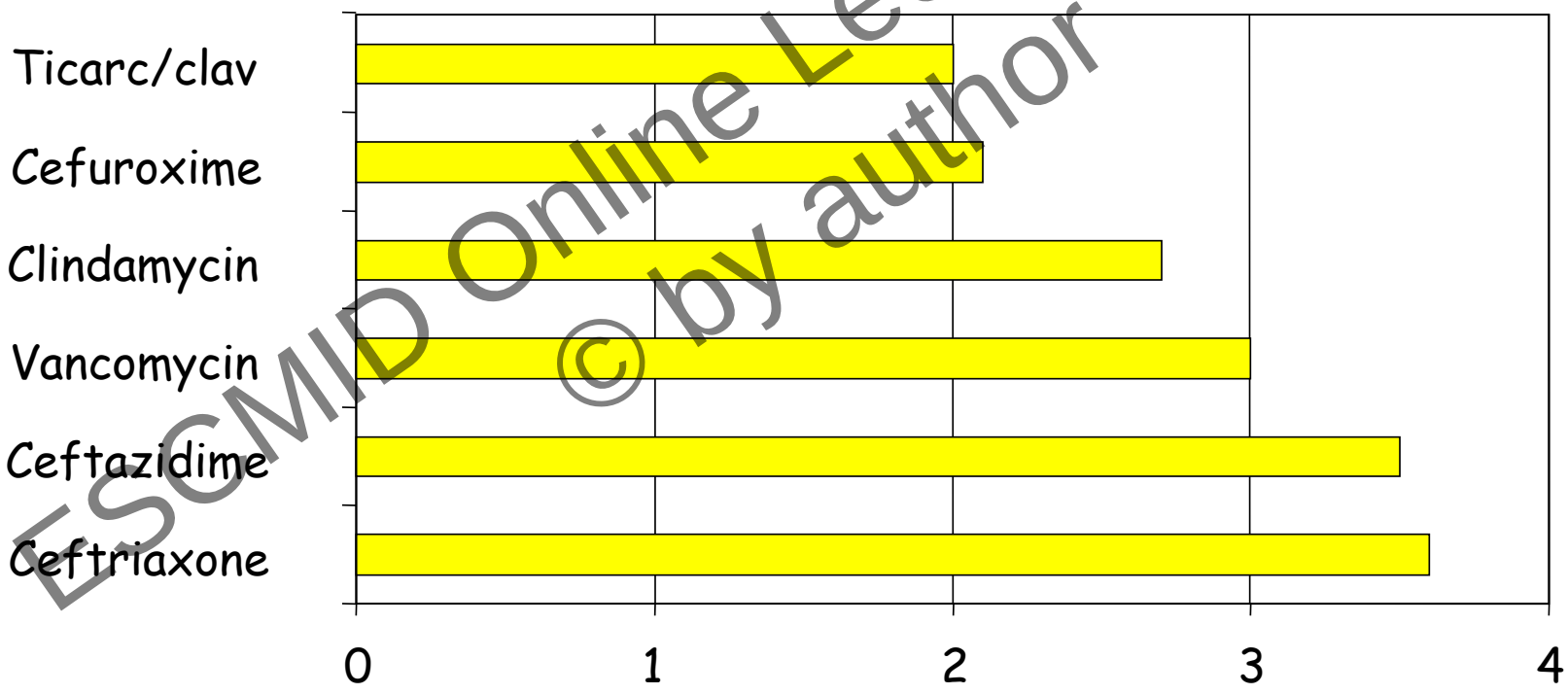
Factors Connected to the Problem of VRE (Colonization and Infection)

- Prolonged hospitalization (>7 days)
- Stay in ICU
- Transplantation
- Haematologic malignancy
- Previous antibiotic use
- Close physical proximity to a patient infected or colonized with VRE…

Gold HS, Clin Infect Dis 2001

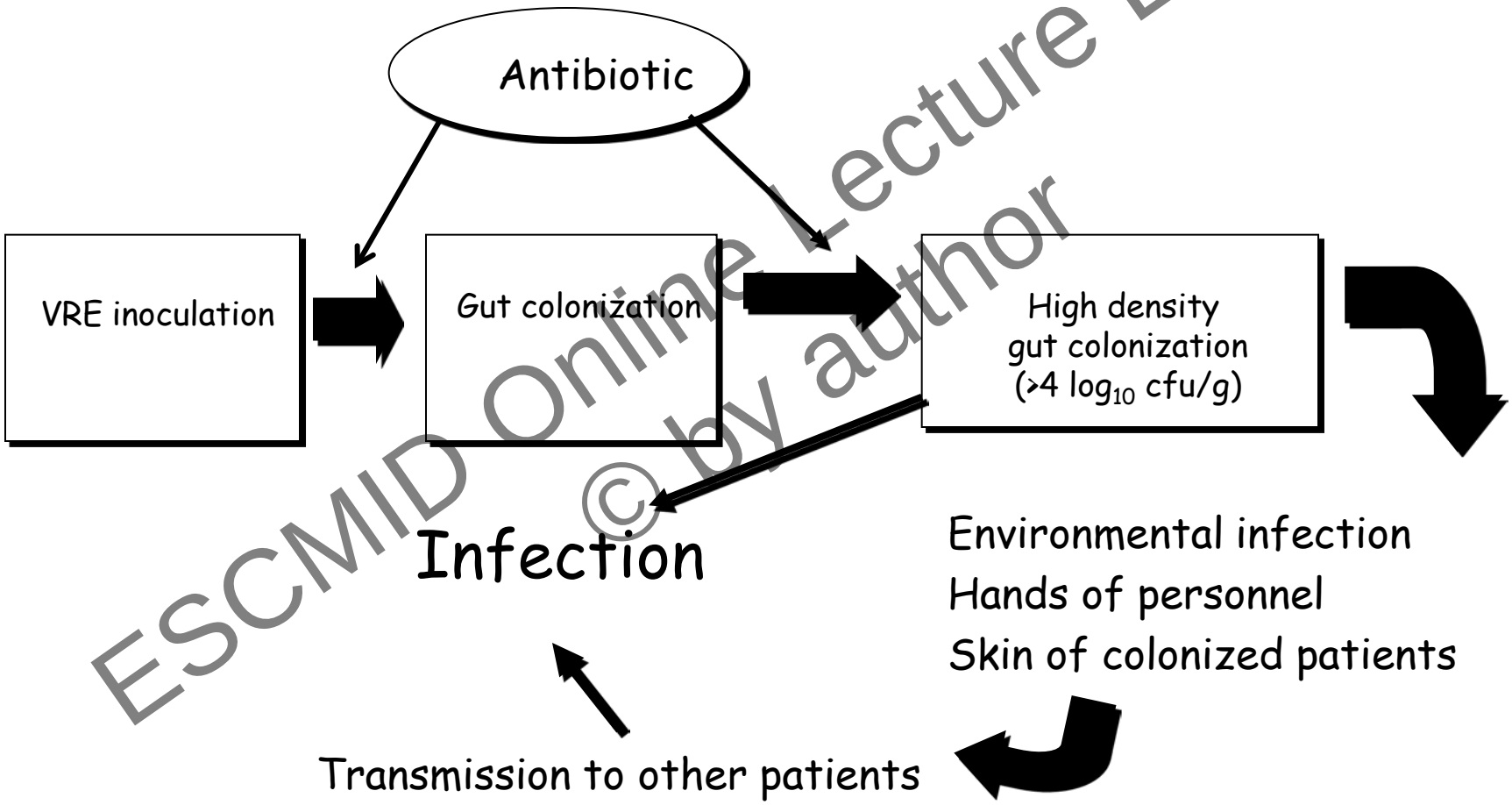
Linden PK, Drugs 2002

Prior Antimicrobial Use: Relative Risk for VRE Colonization



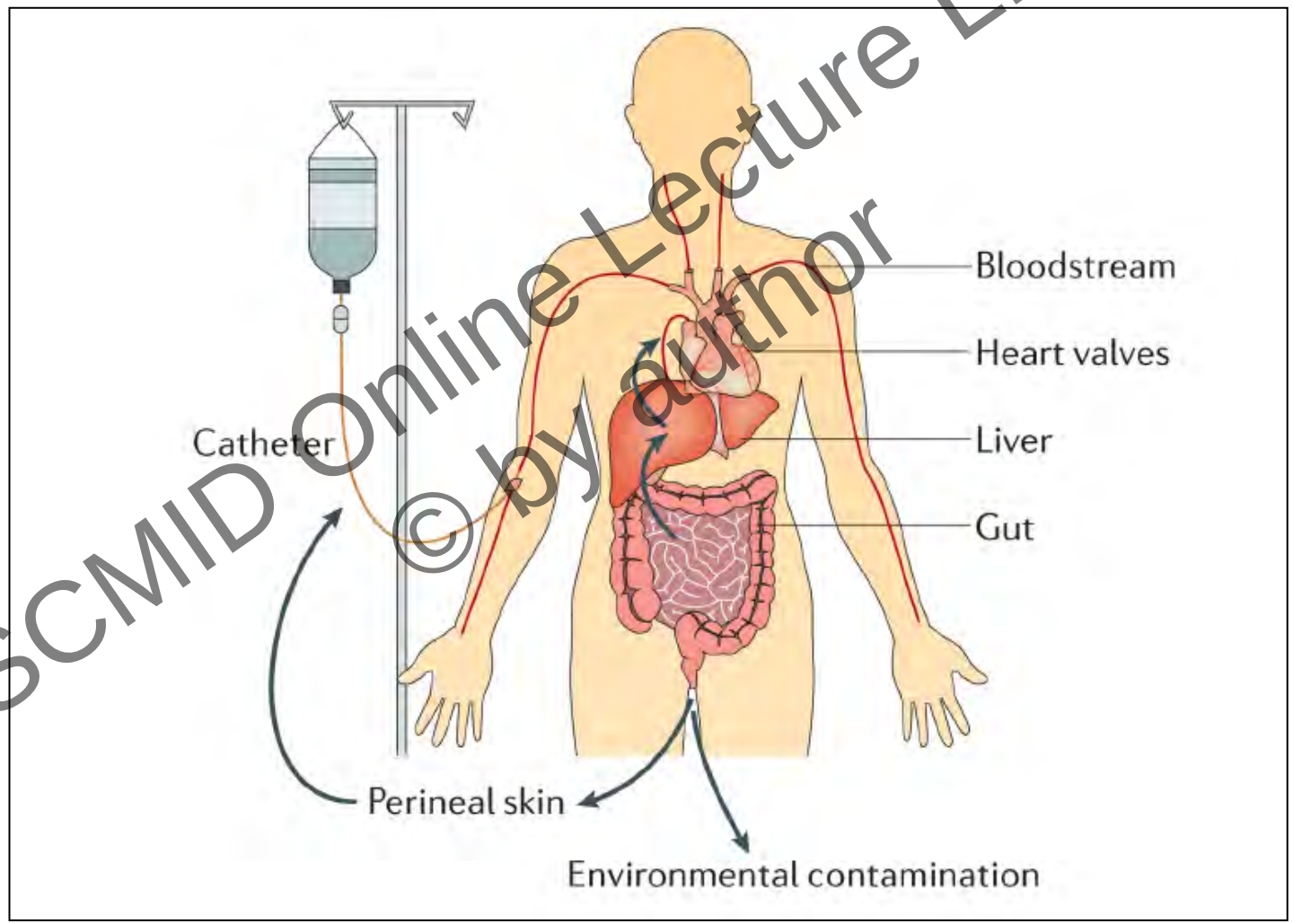
Tokars JI et al, Infect Control Hosp Epidemiol 1999

Gut Colonization and Dissemination of VRE



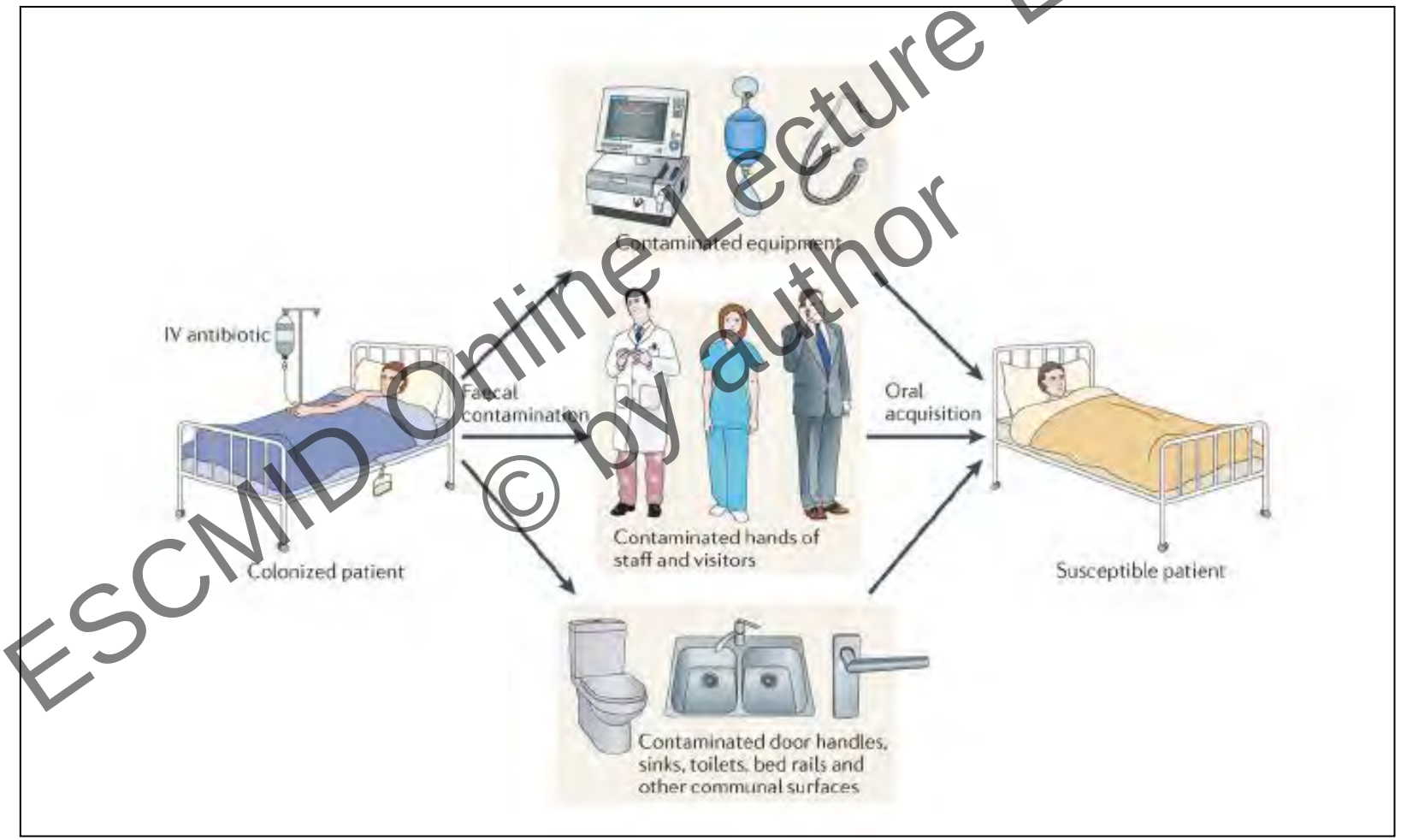
Donskey CJ et al, Clin Microbiol Newsletter 1999

The crucial role of the GI tract in enterococcal infection and spread



Arias CA & Murray BE, Nat Rev Microbiol 2012

Major routes of nosocomial transmission of VRE



Arias CA & Murray BE, Nat Rev Microbiol 2012

Clinical Significance of VRE

- Two separate meta-analyses: VRE vs VSE bacteremia
  - 13 studies
    - VRE bacteremia had increased risk for death (X2.6)
    - 1.8 fold increase in attributable mortality
  - 9 studies
    - Odds ratio 2.5 (CI 1.9-3.4) for death from VRE bacteremia
- In other studies
  - VRE associated with increased LOS and costs of hospital stay
  - The association between mortality and vancomycin resistance is independent of the species

Arias CA & Murray BE, Expert Rev Anti Infect Ther 2008
Chou YY et al, J Microbiol Immunol Infect 2009

Management of the VRE Problem

- Infection control measures
- Antibiotic stewardship measures
  - Restrictions in antibiotic use
  - Proper antibiotic treatment of VRE infections
- Novel antibiotics to overcome resistance(?)

Table 1: Summary of infection prevention and control interventions for patients in hospital

Intervention	Methicillin-resistant *Staphylococcus aureus*	Vancomycin-resistant *Enterococcus*	*Clostridium difficile*–associated disease
Hand hygiene	Required	Required	Required
Cleaning	Required	Required	Required
Housed in a single room	Required	Required	Own toilet
Barriers			
Gloves	Required	Required	Required
Gowns	Required*	Required*	Required
Masks	Required†	Not required	Not required
Screening	Required	Required	Not required

*Facilities may differ as to whether gowns are required for room entry or for contact with patients and their environment.
†Masks are required when a patient with methicillin-resistant *Staphylococcus aureus* has a cough, as part of droplet precautions. Facilities may otherwise differ as to whether masks are required for room entry or patient contact, or both.

Johnston BL & Bryce E, CMAJ 2009

Manipulation of a Hospital Antimicrobial Formulary to Control an Outbreak of Vancomycin-Resistant Enterococci

John Quale, David Landman, Guillermo Saurina, Elaine Atwood, Virginia DiTore, and Keval Patel

From the Departments of Medicine and Infection Control, Department of Veterans Affairs Medical Center, and the Department of Medicine, State University of New York Health Science Center, Brooklyn, New York

Clin Infect Dis (1996); 23 (5): 1020-1025

Antimicrobial treatment in patients with surveillance cultures

Prior antibiotic	No of patients Before intervention (no=192)	After (no=192)	*P* value
Ampicillin	14	6	NS
Amp-sulbactam	0	32	<0.0001
Pip/tazo	0	16	0.0002
Cefazolin	20	18	NS
Cefoxitin	9	7	NS
Cefotaxime	58	3	<0.0001
Ceftazidime	27	10	<0.006
Clindamycin	63	4	<0.0001
Metronidazole	22	30	NS
Gentamicin	16	18	NS
Vancomycin	23	17	NS
Any antibiotic	112	104	NS
Colonized with VRE	91 (47%)	29 (15%)	<0.001

Quale J et al, Clin Infect Dis 1996

Principal and Adjunctive Measures for VRE Infections

Principal measures

- Intravascular catheter removal
- Bladder catheter removal
- Wound debridement
- Percutaneous drainage of deep collection
- Decompression of visceral obstruction
- Surgical drainage/repair
- Retransplantation
- Allograft removal

Adjunctive measures

- Reducing iatrogenic immunosuppression
- Eliminating VRE-selective antimicrobials
- Shortening period of neutropenia

Linden PK, Drugs 2002

Treatment Considerations for Serious VRE Infections

- Problems when composing a synergistic regimen
  - High level resistance to β-lactams
  - High level resistance to aminoglycosides
- Alternatives
  - Dalfopristin - quinupristin (E. faecium only)
  - Linezolid
  - Daptomycin
  - Tigecycline
  - Teicoplanin (Van B)*
  - Investigational drugs (Oritavancin)*

Table IV. Comparison of major features of quinupristin/dalfopristin and linezolid

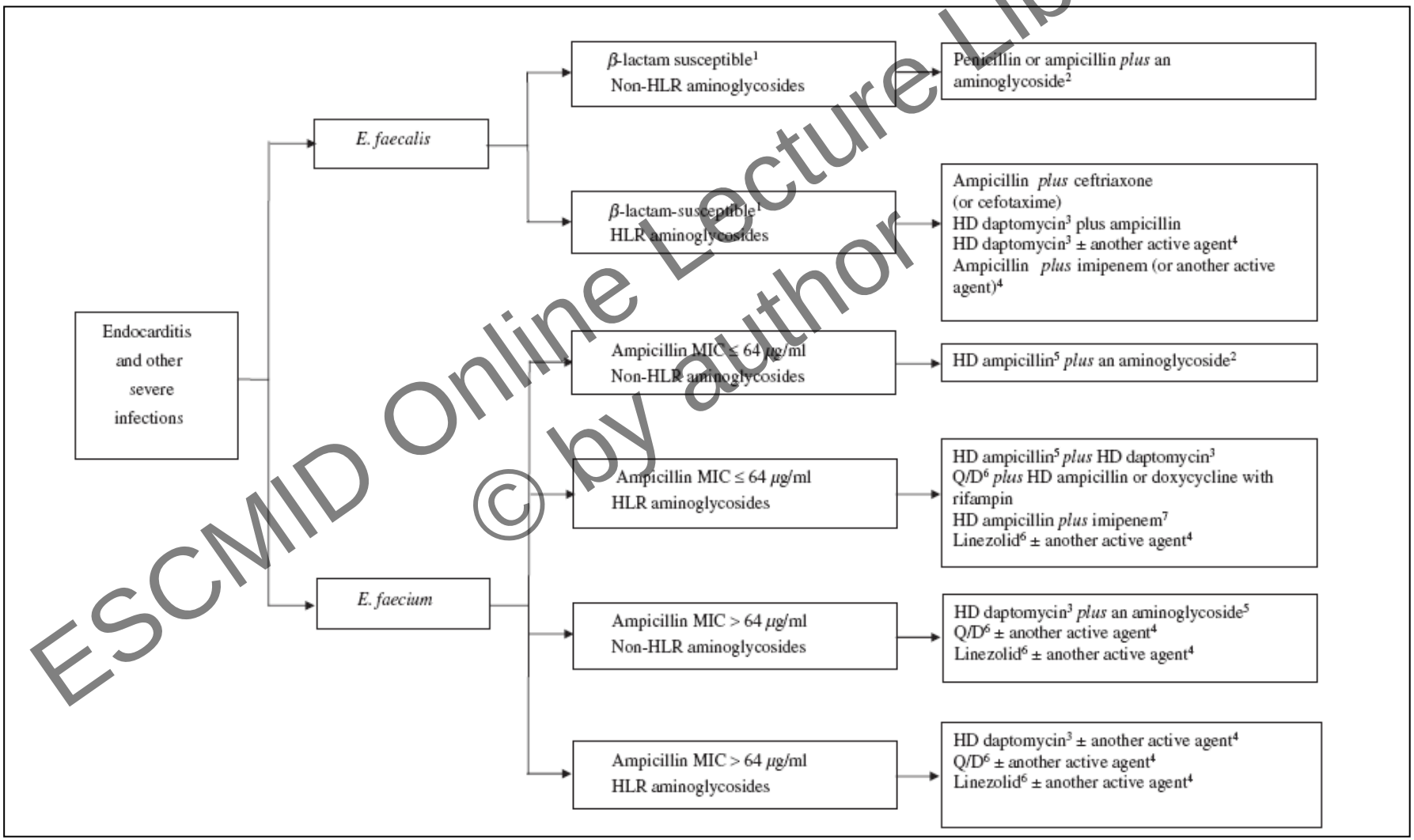
Feature	Quinupristin/dalfopristin	Linezolid
Antimicrobial class	Streptogramin	Oxazolidinone
Peak serum concentrations (mg/L)	10-12	15.1
Elimination half-life (h)	0.8 (Q), 0.6 (D)	5.5
Major metabolic routes	Hepatobiliary	Peripheral non-oxidative
Major elimination routes	Faecal (70-75%)	Nonrenal (65%)
	Urinary (19%)	Urinary (30%)
Protein binding (%)	30 (Q) 70 (D)	31
Mechanism of action	Protein synthesis inhibition	Protein Synthesis inhibition
Site of action	50S Ribosome	70S Initiation Complex
Post-antibiotic effect (h)	6-8	1
Bactericidal (*vs* VRE)	No	No
Cytochrome P-450 inhibition	Yes	No
Formulations	Parenteral	Parenteral + Oral
Dose and administration	5-7.5 mg/kg q 8-12h	600mg q 12h
Dosage adjustment	None	None
Approved indications	VRE	VRE
	Complicated SSSI	Complicated SSSI
	Nosocomial pneumonia	Nosocomial pneumonia
Major adverse effects	Phlebitis (peripheral)	Myelosuppression
	Myalgia/arthralgia	
Cost ($US per day; 2000 values)	$300-350	$115 (parenteral)
		$80 (oral)

D = dalfopristin; **Q** = quinupristin; **qXh** = every X hours; **SSSI** = skin and skin structure infection; **VRE** = vancomycin-resistant enterococci.

Linden PK, Drugs 2002

Figure 4.40: *Enterococcus faecalis*: percentage (%) of invasive isolates with high-level resistance to aminoglycosides, by country, EU/EEA countries, 2011

Suggested Therapeutic Alternatives in Serious VRE Infections



Arias CA et al, Clin Microbiol Infect 2010

Therapeutic Options for Less Serious VRE Infections

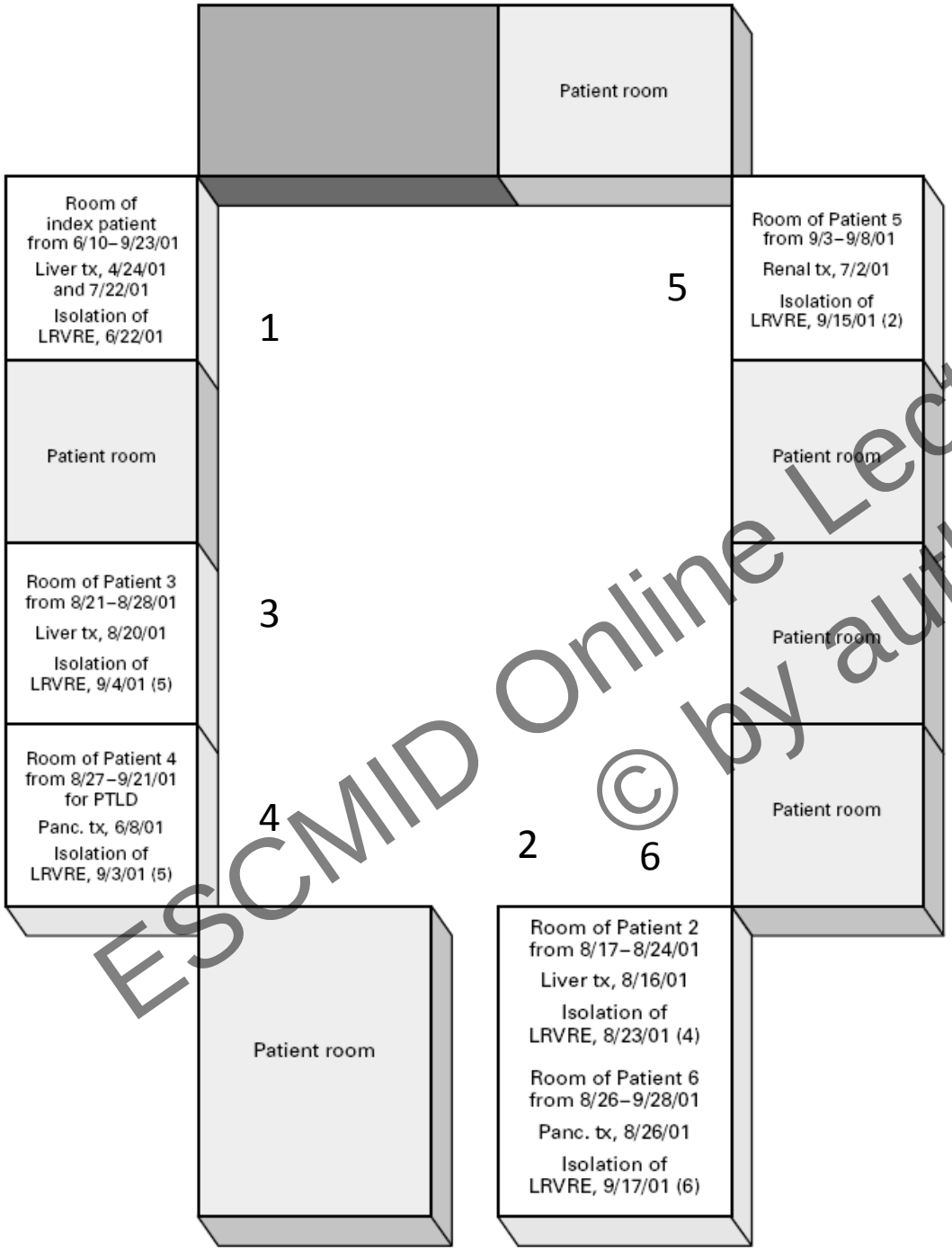
- Nitrofurantoin
- Fosfomycin
- Tetracyclines (doxycycline, minocycline)
- Quinolones…

Arias CA et al, Clin Microbiol Infect 2010

Linezolid for VRE Infections

- Approved for VRE infections
- Frequently used even though the relevant clinical data is scarce
- Resistance usually due to the G2576T mutation, however plasmid mediated in some cases (cfr methyltransferase)
- Resistant strains found in patients without prior exposure to the drug
- Resistance rates up to 15% in some institutions

Cattoir V & Leclercq R, J Antimicrob Chemother 2013
Santayana EM et al, Diagn Microbiol Infect Dis 2012



Spread of Linezolid – Resistant VRE in a transplantation unit

- Emergence of LinR – VRE in the index case, after treatment with linezolid of an intra - abdominal infection due to a LinS - VRE strain

- No other patient received linezolid!!!

Herrero IA et al, N Engl J Med 2002

Daptomycin for VRE infections

- Not approved for use
- For CLSI, susceptible if MIC ≤4µg/ml
- Efficiency shown in retrospective studies
- Synergy with rifampin (E. faecium), gentamicin (E. faecalis)
- Optimal dosage?
- Reports of emergence of resistance during treatment are worrisome

Arias CA et al, Clin Microbiol Infect 2010

Cattoir V & Leclercq R, J Antimicrob Chemother 2013

Tigecycline for VRE Infections

- Approved for VSE (E. faecalis), but not VRE
- Expected to be active
- Bacteremia (?)
- Possible role in combination therapies

Arias CA et al, Clin Microbiol Infect 2010

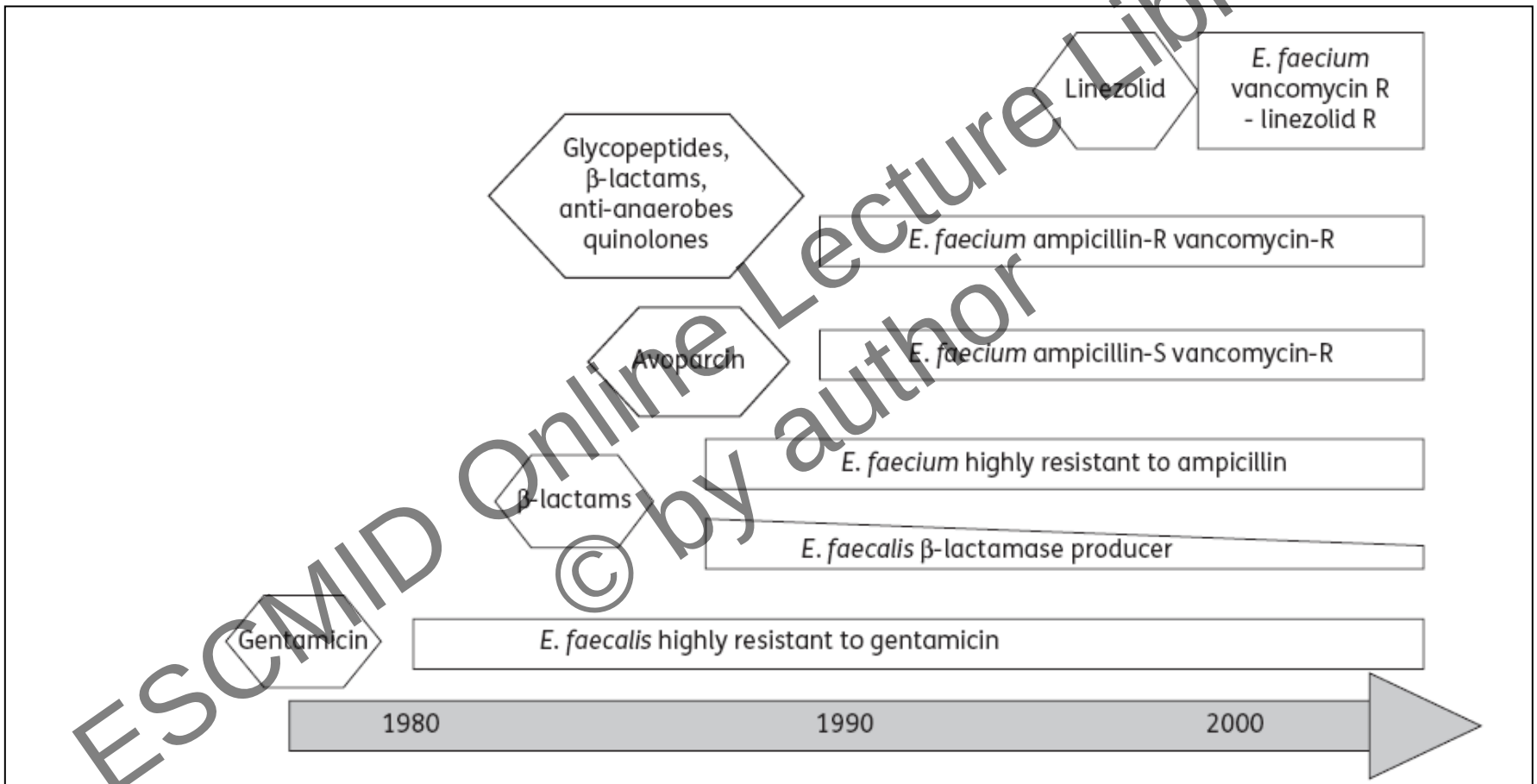


Figure 3. The walk of enterococci towards multiple antibiotic resistance. Selector antibiotics are shown in the lozenges.

Cattoir V & Leclercq R, J Antimicrob Chemother 2013

VRE: Collateral Damage

- Transfer of the VanA operon to S. aureus resulting in VRSA (Michigan, USA, 2002)

Chang S et al, N Engl J Med 2003

Conclusions (1)

- VRE is a worldwide issue, in a considerably different degree in various countries
- Important characteristics
  - Persistence
  - Plasticity of genome (easy incorporation of resistance material)
- When present, is a very serious problem due to
  - Difficulty in eradication
  - Limited options for the treatment of infections
  - Bad quality of infected patients

Conclusions (2)

- Strict infection control and antibiotic stewardship measures are of paramount importance in order to tackle the VRE problem
- New antibiotics are needed as well as ways to reduce or prevent colonization