Principi di trattamento empirico e mirato delle infezioni batteriche e fungine postoperatorie

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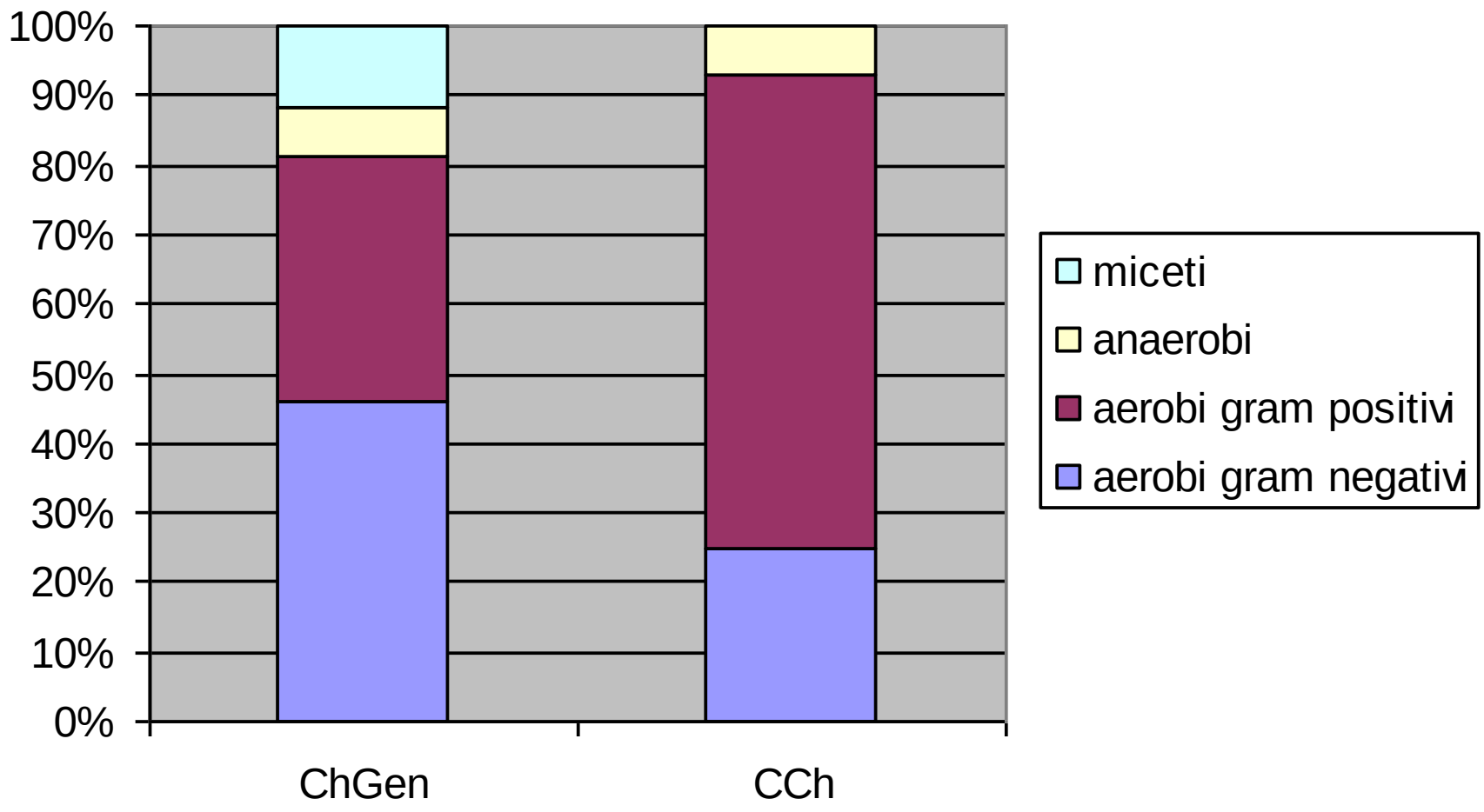
Major pathogens in SSI

Pathogen	% of infections
S.aureus	20
CoNS	14
Enterococchi	12
E.coli	8
P.aeruginosa	8
Enterobacter spp.	7
P.mirabilis	3
K.pneumoniae	3
Altri streptococchi	3
C.albicans	2
Streptococchi gruppo D	2
Bacteroides fragilis	2
Altri Gram negativi aerobi	2
Citrobacter spp	1
S.marcescens	1
Candida spp.	1
Gram positivi anaerobi	1

NNISS – January 1990 – March 1996

Distribuzione degli isolati da materiali provenienti dal sito chirurgico in reparti di chirurgia generale e cardiochirurgia



Distribuzione degli isolati Gram positivi da materiali provenienti dal sito chirurgico in reparti di chirurgia generale e cardiochirurgia

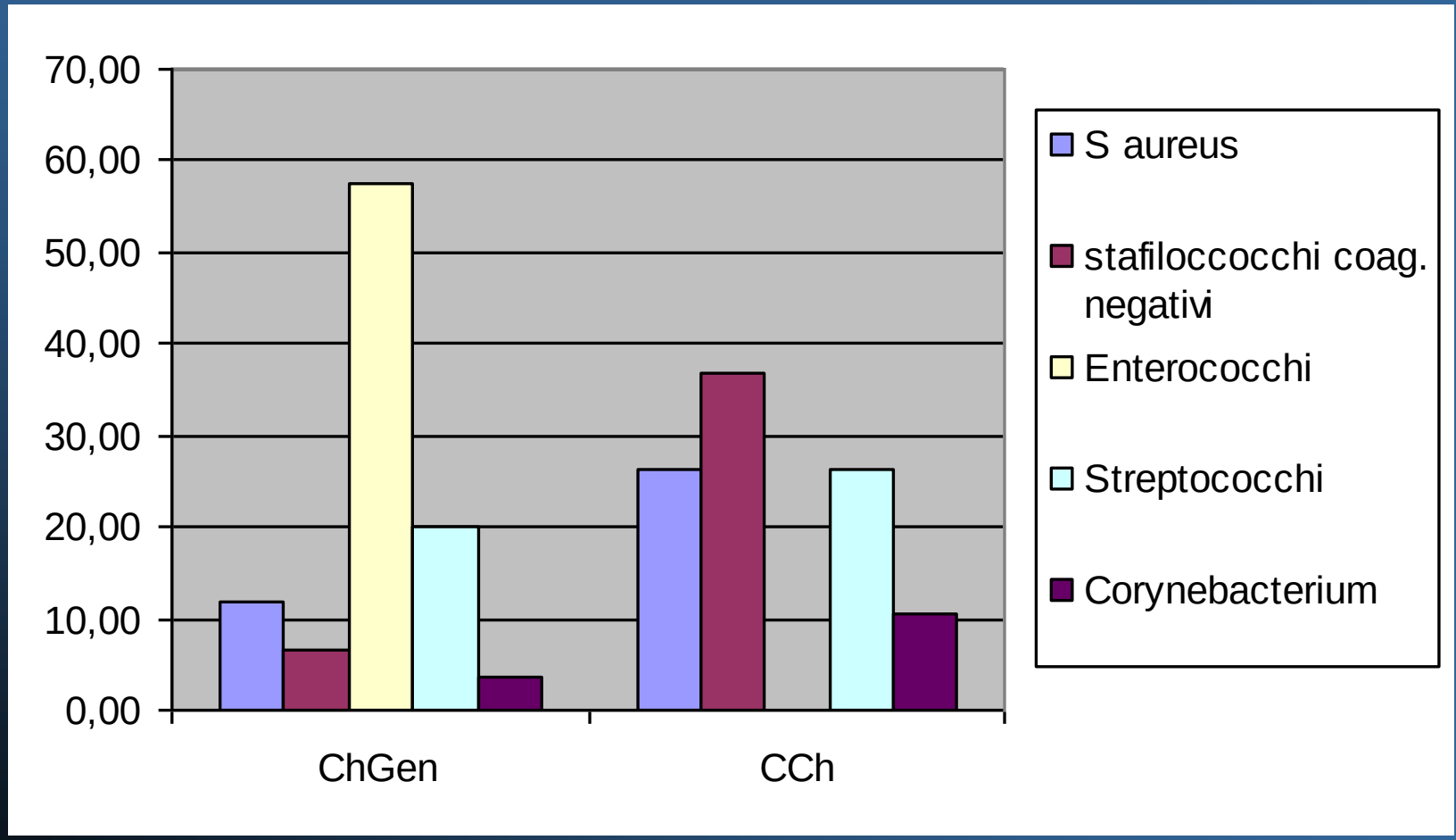


Table 2. Surgical site infection rates for most common operative procedure categories and risk-adjusted comparisons with rates from international surveillance systems

NNIS operative category	No. of SSI/procedures	SSI rate	95% CI	US rates[3] SIR	US rates[3] P value	Spanish rates[4] SIR	Spanish rates[4] P value	Italian rates[12] SIR	Italian rates[12] P value	Italian rates[13] SIR	Italian rates[13] P value
Open reduction of fracture	10/251	4.0	1.9-7.2	3.6	<.001	1.5	.144				
Vascular surgery	13/242	5.4	2.9- 9.0	3.0	<.001	1.3	.163	1.3	.178		
Other musculoskeletal system	7/232	3.0	1.2- 6.1	3.6	.004	0.9	.438	1.0	.550		
Cholecystectomy	8/200	4.0	1.7-7.7	5.1	<.001	1.8	.077	1.4	.200	1.0	.529
Mastectomy	5/142	3.5	1.2-8.0	1.8	.140	1.4	.279	1.9	.126	0.8	.359
Other endocrine system	3/123	2.4	0.5-6.9	7.3	.009	3.2	.070			1.0	.566
Knee prosthesis	1/117	0.9	0.0-4.7	0.8	.621	0.4	.326				
Herniorrhaphy	1/112	0.9	0.0-4.9	0.6	.541	0.5	.351	0.3	.130	0.2	.056
Thoracic surgery	3/100	3.0	0.6-8.5	3.9	.043	0.8	.444				
Spinal fusion	5/89	5.6	1.9-12.6	2.5	.056	1.4	.291				
Other digestive system	8/83	9.6	4.3-18.1	3.7	.002	1.5	.152			3.1	.005
Other integumentary system	5/76	6.6	2.2-14.7	5.1	.003	1.9	.132	0.8	.409		
Other joint prosthesis	2/69	2.9	0.3-10.1	4.7	.069	1.9	.282				
Gastric surgery	8/69	11.6	5.1-21.6	3.3	.004	2.2	.036			2.4	.019
Colon surgery	10/69	14.5	7.2-25.0	2.5	.009	1.0	.526	0.8	.339	1.2	.355
Craniotomy	7/63	11.1	4.6-21.6	7.0	<.001	5.9	<.001				
Laparotomy	6/50	12.0	4.5-24.3	3.6	.007	1.2	.397			1.4	.225
Other nervous system	1/49	2.0	0.0-10.9	1.3	.528	5.2	.174	0.7	.585		
Hip prosthesis	2/47	4.3	0.5-14.5	3.6	.107	1.2	.476	2.5	.192		
Laminectomy	1/44	2.3	0.0-12.0	2.1	.373	1.1	.581	0.9	.709		
Other Categories*	23/193	11.9	7.7-17.3								

NNIS, National Nosocomial Infection Surveillance system; *SSI*, surgical site infection; *CI*, confidence interval; *SIR*, standardized infection ratio.
*Includes 12 operative categories involving less than 40 procedures each.

SSI at a tertiary care hospital in Greece
Roumbelaki RN et al AJIC 2008;36:732-8

DATI MICROBIOLOGICI

70.5% SSI
Coltura positiva

37.4%
polimicrobica

33.1%
monomicrobica

52.1% Gram positivi

-15.3% *S.epidermidis*
-6.9% *S.aureus*
-12.5% *E. faecium*
-10.4% *E.faecalis*

38.2% Gram negativi

-9.7% *E.coli*
-9.7% *P.aeruginosa*
-5.6% *A.baumannii*

5.5% anaerobi

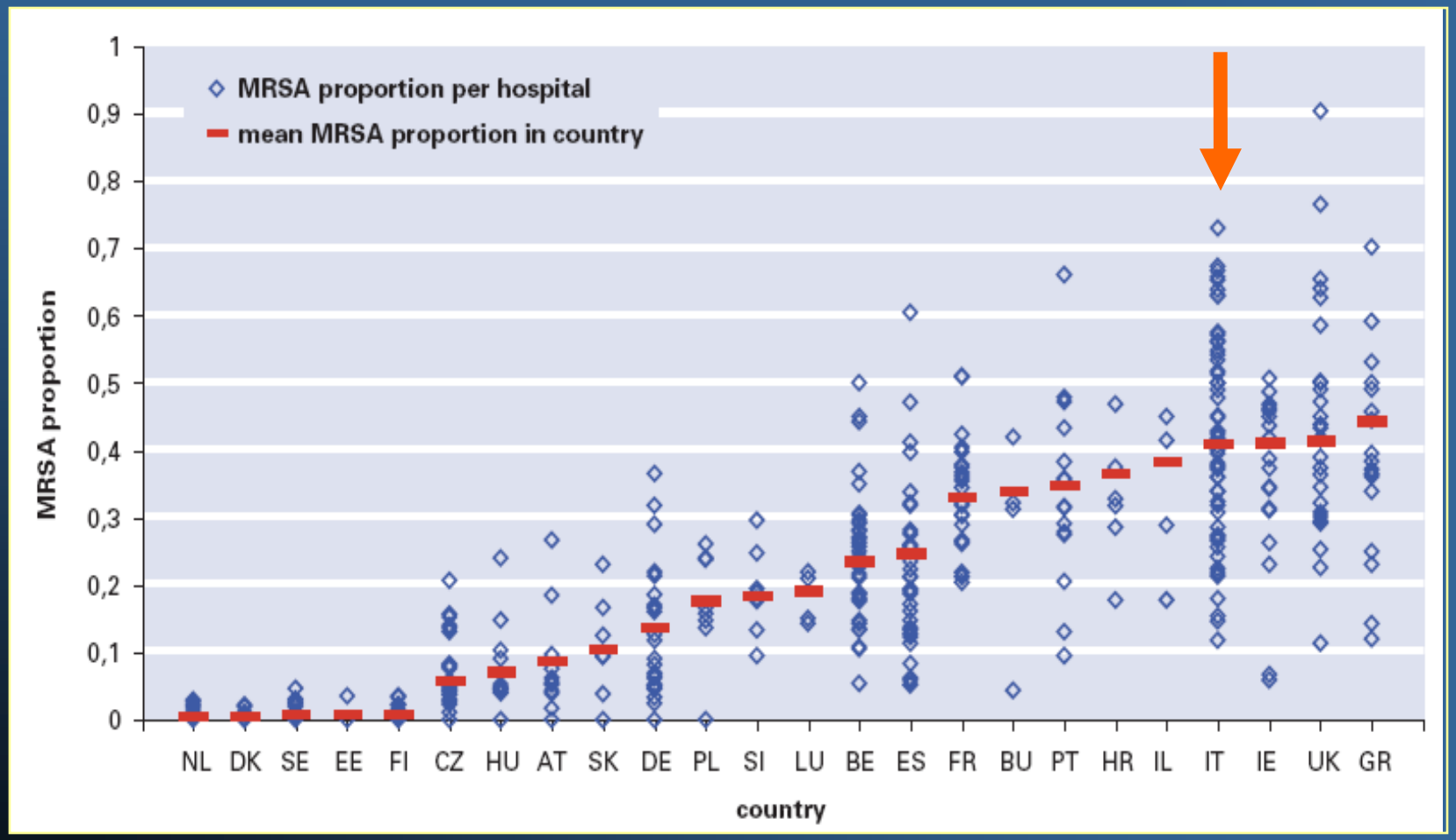
4.2% *Candida spp*

Roumbelaki RN et al AJIC 2008;36:732-8

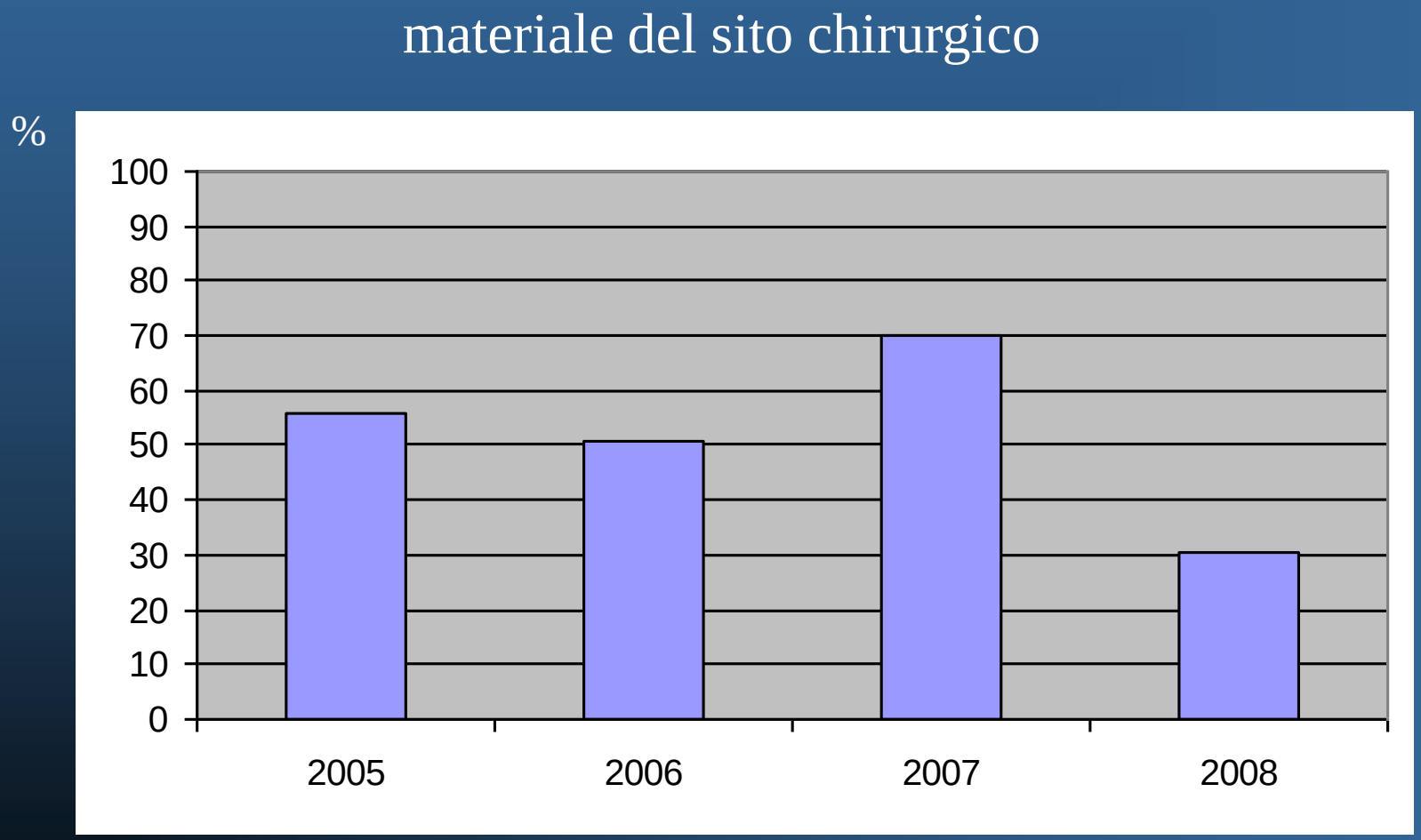
EVOLUTION OF RESISTANCE IN S. AUREUS

1940:	Benzylpenicillin (penG) introduced
1948:	ß-lactamase-positive strains predominate
1950s:	Resistant to all available agents
1960s:	Semi-synthetic penicillins introduced
1961:	Methicillin-resistant strains appeared
1970s:	Multidrug-resistant (MDR) MRSA strains detected
1980s:	Global spread of MDR MRSA
1990s:	Increasing MRSA in hospitals, sporadic nosohusial cases
1997:	VISA and hVISA (*S.aureus* with reduced vancomycin susceptibility)
1998:	CA-MRSA – no link to healthcare institutions
2002:	VRSA (VanA)

MRSA in Ospedale – EARSS 2004



Frequenza degli *S. aureus* oxacillino-R



Vancomycin MIC “creep” – USA data

	number	MIC_{50}	MIC_{90}	N(%) MIC > 1.0
1985 MSSA	30	0.06	0.12	1/30 (3)*
2004 MSSA	25	2.0	2.0	25/25 (100)*
1985 MRSA	25	0.12	0.25	2/25 (8)*
2004 MRSA	28	2.0	2.0	25/28 (89)*

* P< 0.0001 - Kapadia M. et al 45˚ ICAAC abs E-807

Percentage of hVISA by PAP/AUC at different MICs of vancomycin and teicoplanin

DRUGS and MICs	n. of hVISA isolates	Total n. of isolates	% hVISA
Vancomycin			
<0.5	0	4	0
0.5	3	94	3.2
1	52	858	6.1
2	44	381	11.6
4	11	13	84.6
>4	0	1	0
Teicoplanin			
<0.25	0	14	0
0.25	2	271	0.7
0.5	9	578	1.6
1	31	322	9.6
2	38	123	30.9
4	7	16	43.8
>4	13	23	56.5

Rybak MJ et al JCM 2008; 46:2950; Tenover ICAAC 2006

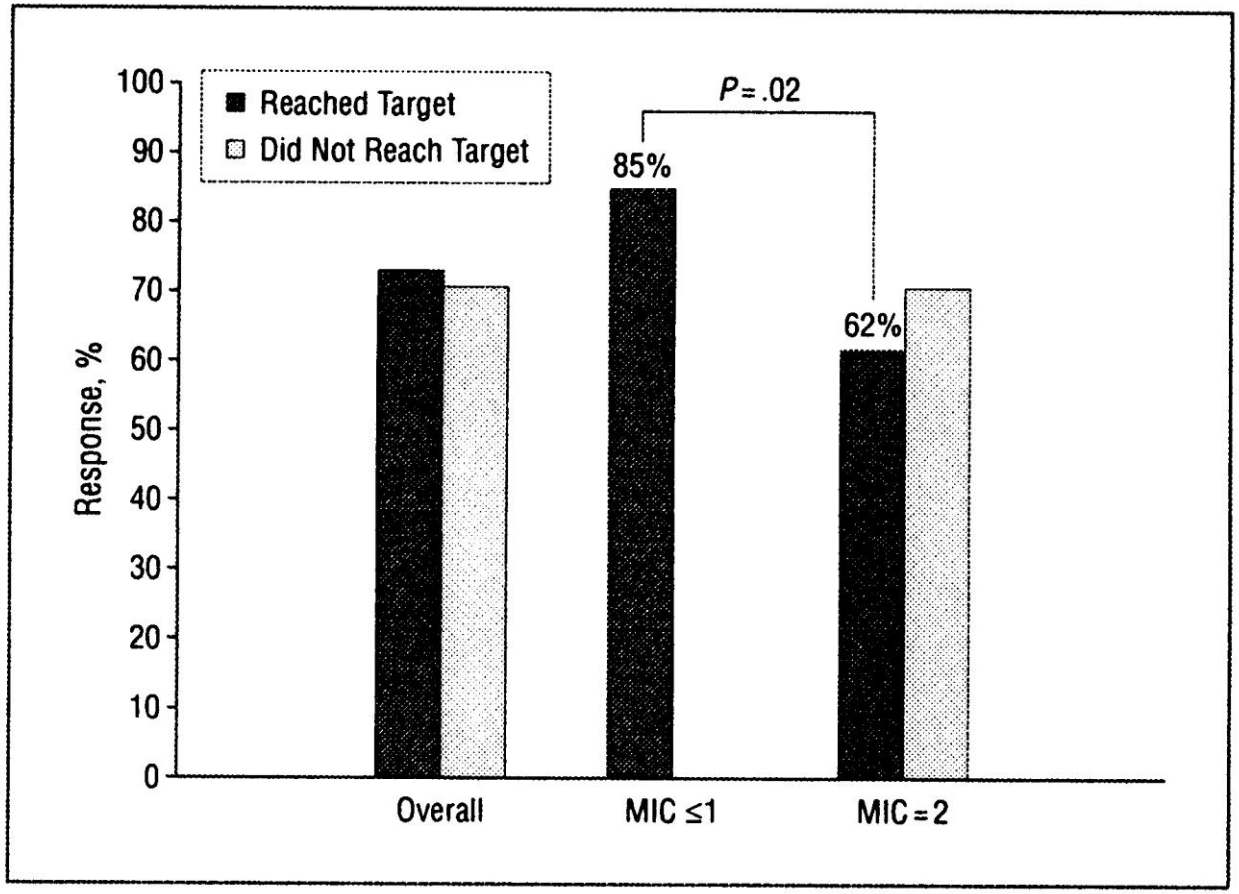
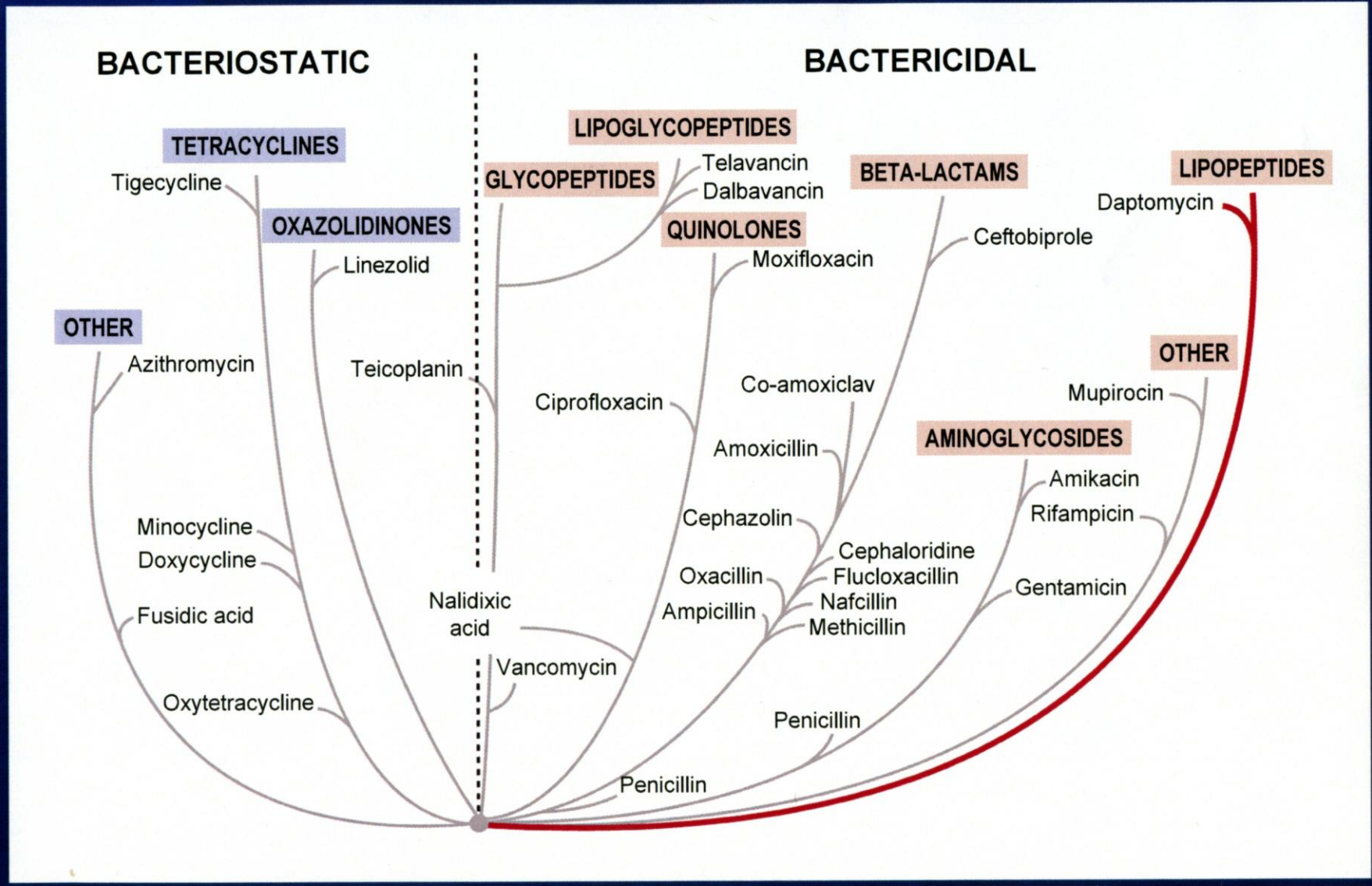


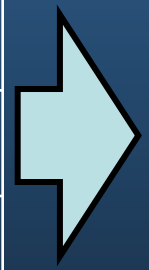
Figure 2. Final response based on target trough achievement. Evaluation was based on 86 patients (9 patients were excluded because of change in therapy from vancomycin hydrochloride). MIC indicates minimum inhibitory concentration.

Bactericidal and bacteriostatic antibiotics

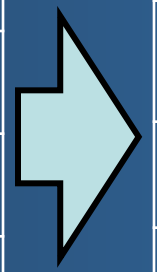


ANTIBIOTICI AD ATTIVITA' ANTISTAFILOCOCCICA

MS
OXACILLINA
CEFAZOLINA
RIFAMPICINA
COTRIMOXAZOLO



MR
VANCOMICINA
TEICOPLANINA
MINOCICLINA
COTRIMOXAZOLO
ACIDO FUSIDICO
RIFAMPICINA



MR/GISA
LINEZOLID
DAPTOMICINA
TIGECICLINA
DALBAVANCINA
CEFTOBIPROLO
TELAVANCINA
ORITAVANCINA

GLICOPEPTIDI

VANTAGGI	LIMITI
➢Uso consolidato	➢Posologia (vanco 1x2, 500x4, PC.; teico 6-12 mg/kg)
➢Tollerabilità (teico)	➢Aumento MIC? (vanco e teico??)
➢Resistenza limitata	➢Diffusibilità tissutale
➢Costi (vanco)	➢Attività batteriostatica/battericida
	➢Necessità dose da carico (teico)

LINEZOLID

VANTAGGI	LIMITI
➢Diffusibilità tissutale	➢Effetto batteriostatico
➢Attività su Gram positivi multiresistenti	➢Tollerabilità
➢Spettro ristretto	➢Limitate indicazioni (uso off label?)
	➢Costo

DAPTOMICINA

VANTAGGI	LIMITI
➢Effetto battericida	➢Inattività nelle RTI
➢Tollerabilità	➢Posologia (4-6-8?)
	➢Limitate indicazioni (uso off label?)
	➢Costo

TIGECICLINA

VANTAGGI	LIMITI
➢Ampio spettro	➢Ampio spettro
➢Attività su germi multiresistenti	➢Effetto batteriostatico
➢Diffusibilità tissutale	➢Tollerabilità G.I.
➢Limitate indicazioni	➢Limitate indicazioni (uso off label?)
	➢Costo

APPROCCIO TRADIZIONALE ALLA TERAPIA DEI GRAM POSITIVI DI ORIGINE NOSOCOMIALE

MICRORGANISMO	TERAPIA DI SCELTA
MSSA	Oxacillina ± gentamicina
MRSA	Vancomicina o Teicoplanina ± Gentamicina o Rifampicina Linezolid Daptomicina Tigeciclina

TERAPIA DELLE INFEZIONI SOSTENUTE DA GISA O VISA

- COTRIMOXAZOLO
- MINOCICLINA
- RIFAMPICINA
- VANCOMICINA + BETALATTAMINE

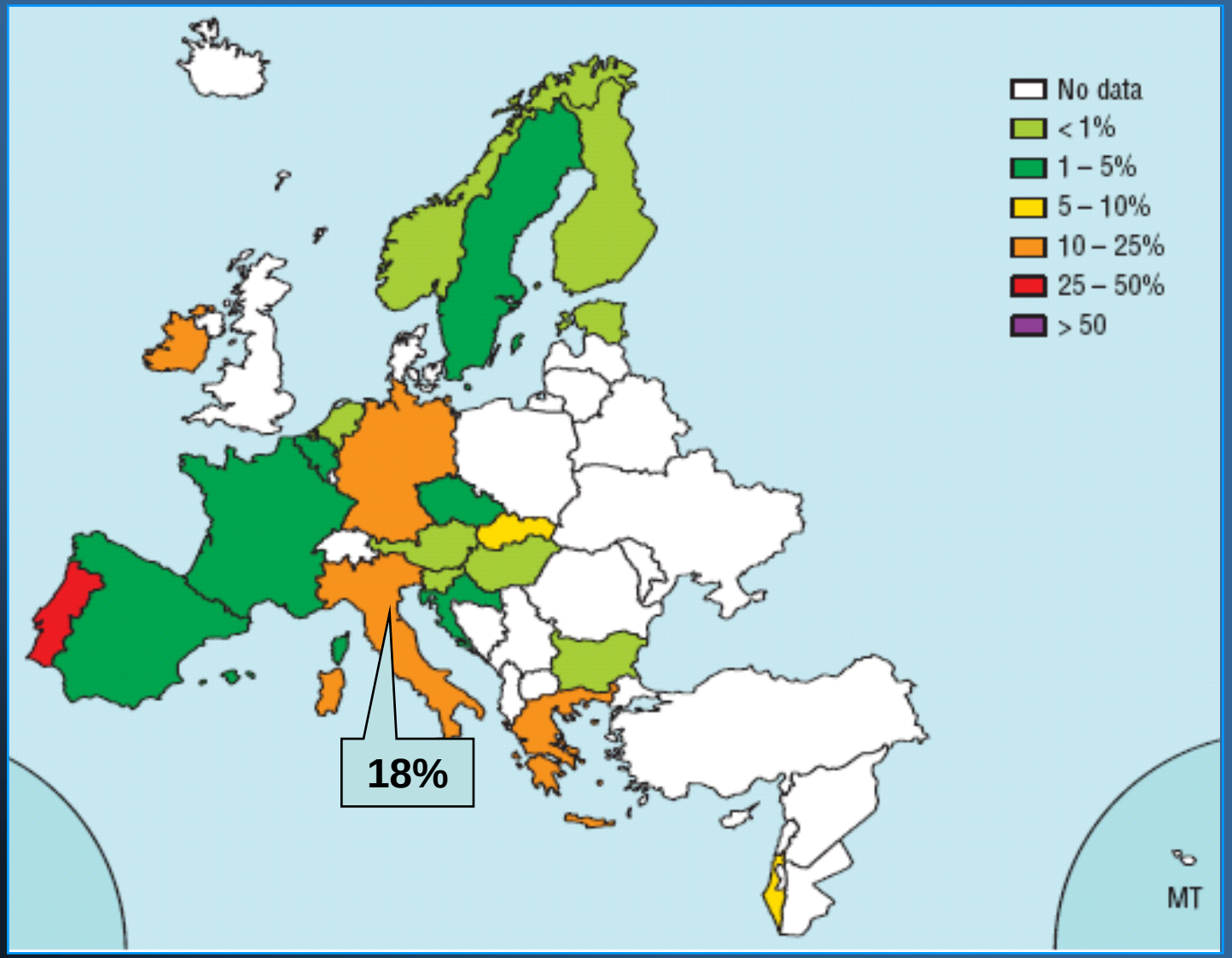
- LINEZOLID
- SYNERCID
- DAPTOMICINA
- TIGECICLINA

MMWR 51: 902, 2002, NEJM 348 1342 2003; CID 32: 108 2001

CONOLOGIA DELLE RESISTENZE ACQUISITE NEGLI ENTEROCOCCHI

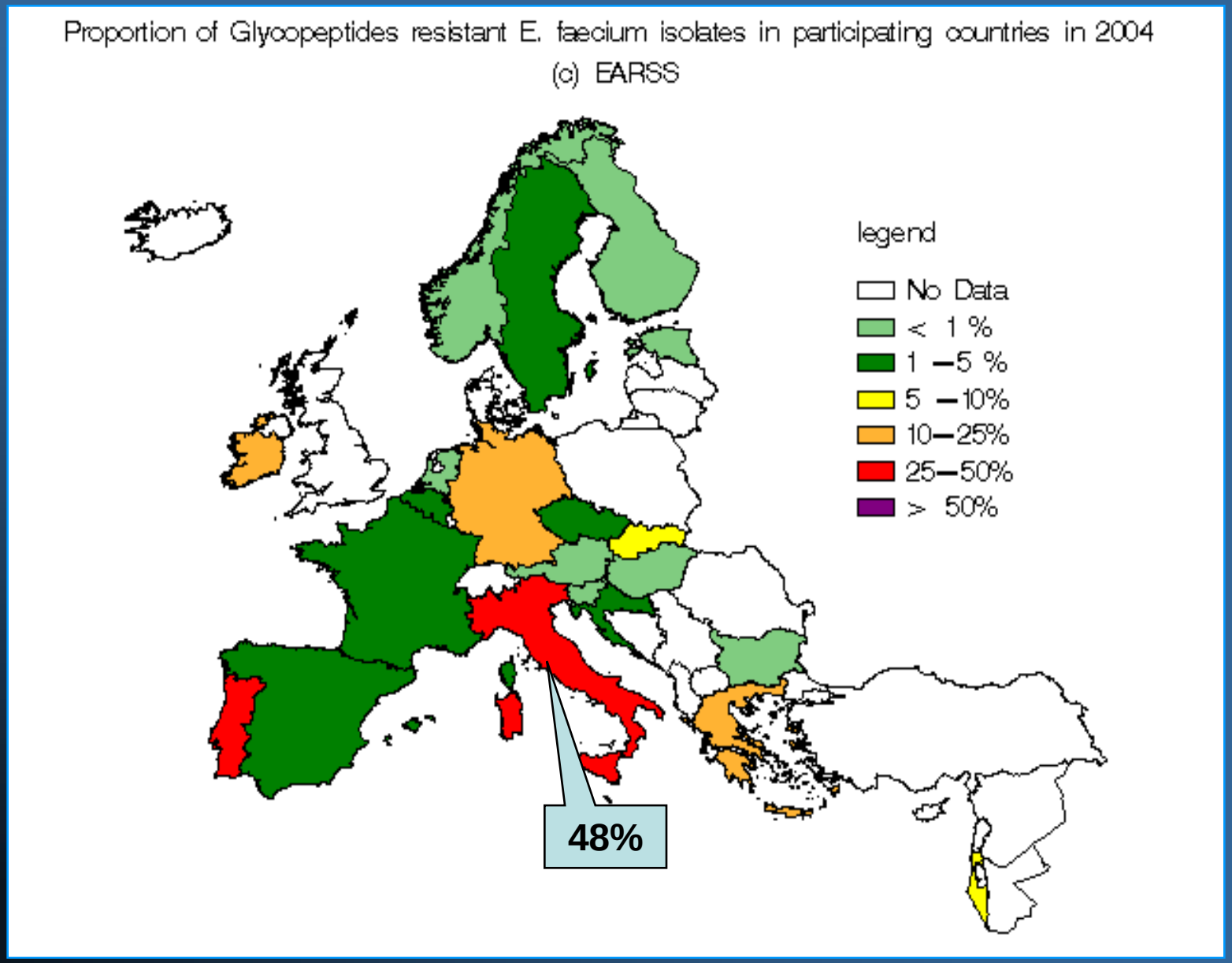
- 1970 : alta resistenza alla Streptomicina (1954)
- 1979 : alta resistenza alla Gentamicina
- 1983 : βeta-lattamasi
- 1986 : glicopeptidi (Vancomicina, Teicoplanina)
- 1989 : alta resistenza a Penicillina e Ampicillina
- 1991 : resistenza a tutti gli agenti disponibili

Vancomycin resistant *E. faecium* (invasive isolates)

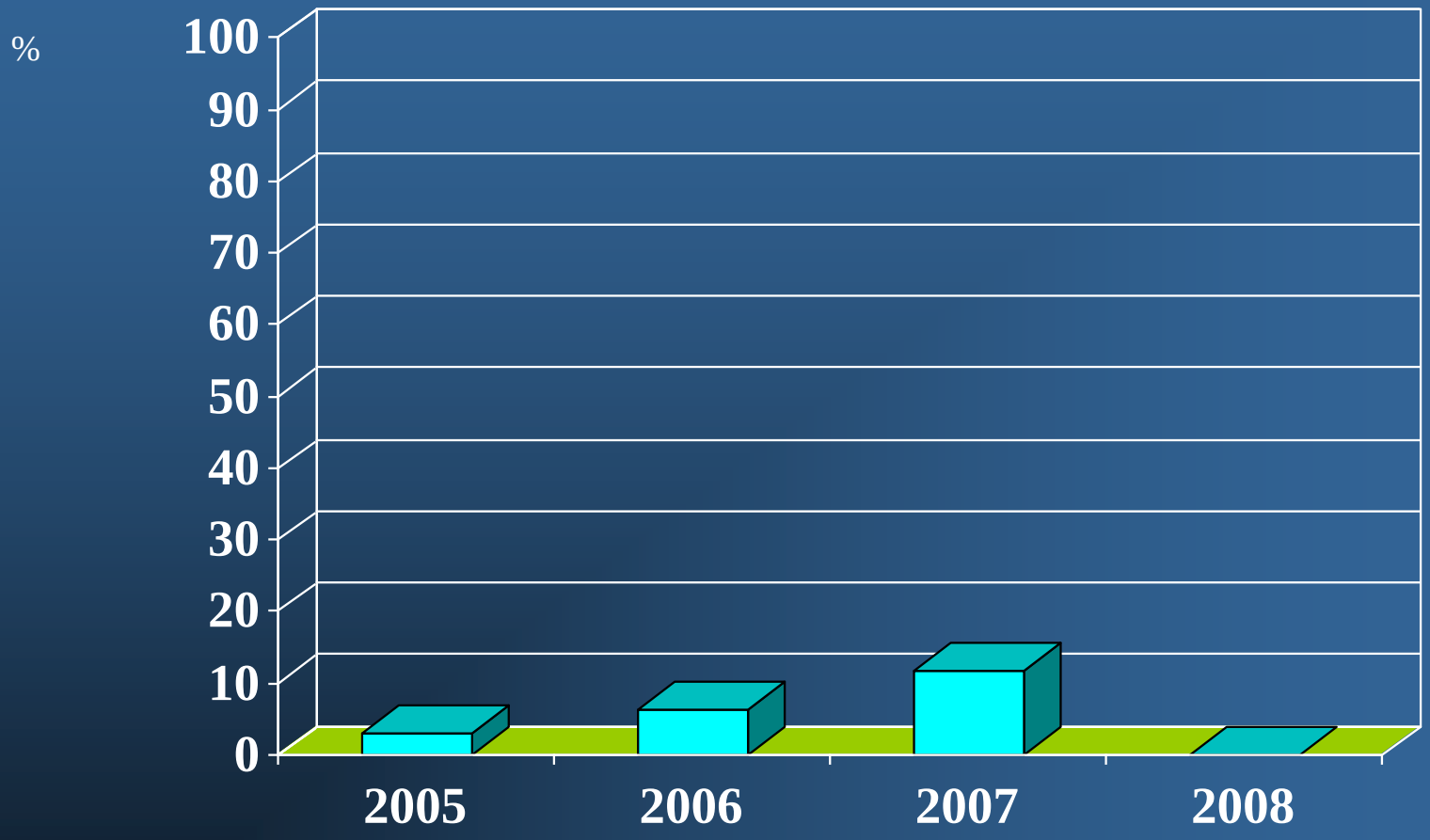


EARSS Annual Report, 2006

Promotion of Aminoglyc High resistant E. faecium isolates in participating countries in 2006 (c) EARSS



Frequenza degli *E. faecium* vancomicino-R



Incidenza per 1000 giorni paziente	**0.03**	**0.08**	**0.18**	**0**

TERAPIA DEI VRE

E. FAECALIS

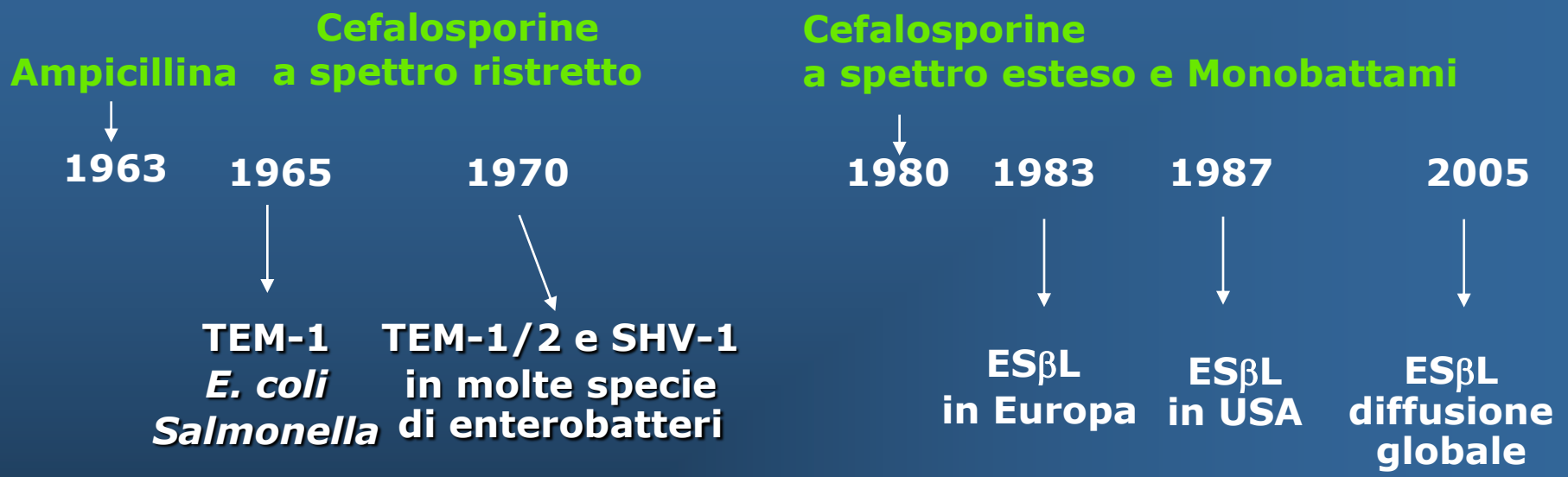
- **NITROFURANTOINA (UTI) LINEZOLID**
- **DAPTOMICINA**
- **TIGECICLINA**

E. FAECIUM

- **NITROFURANOINA (UTI)**
- **LINEZOLID**
- **SYNERCID**
- **DAPTOMICINA**
- **TIGECICLINA**

JAC 52: 123 2003, NEJM 342: 710 2000, JAC 53:646,2004; NEJM 346:867 2002, CIRCULATION 111 e 394 2005

Evoluzione della resistenza ai b-lattamici nelle *Enterobacteriaceae* mediata dalle b-lattamasi

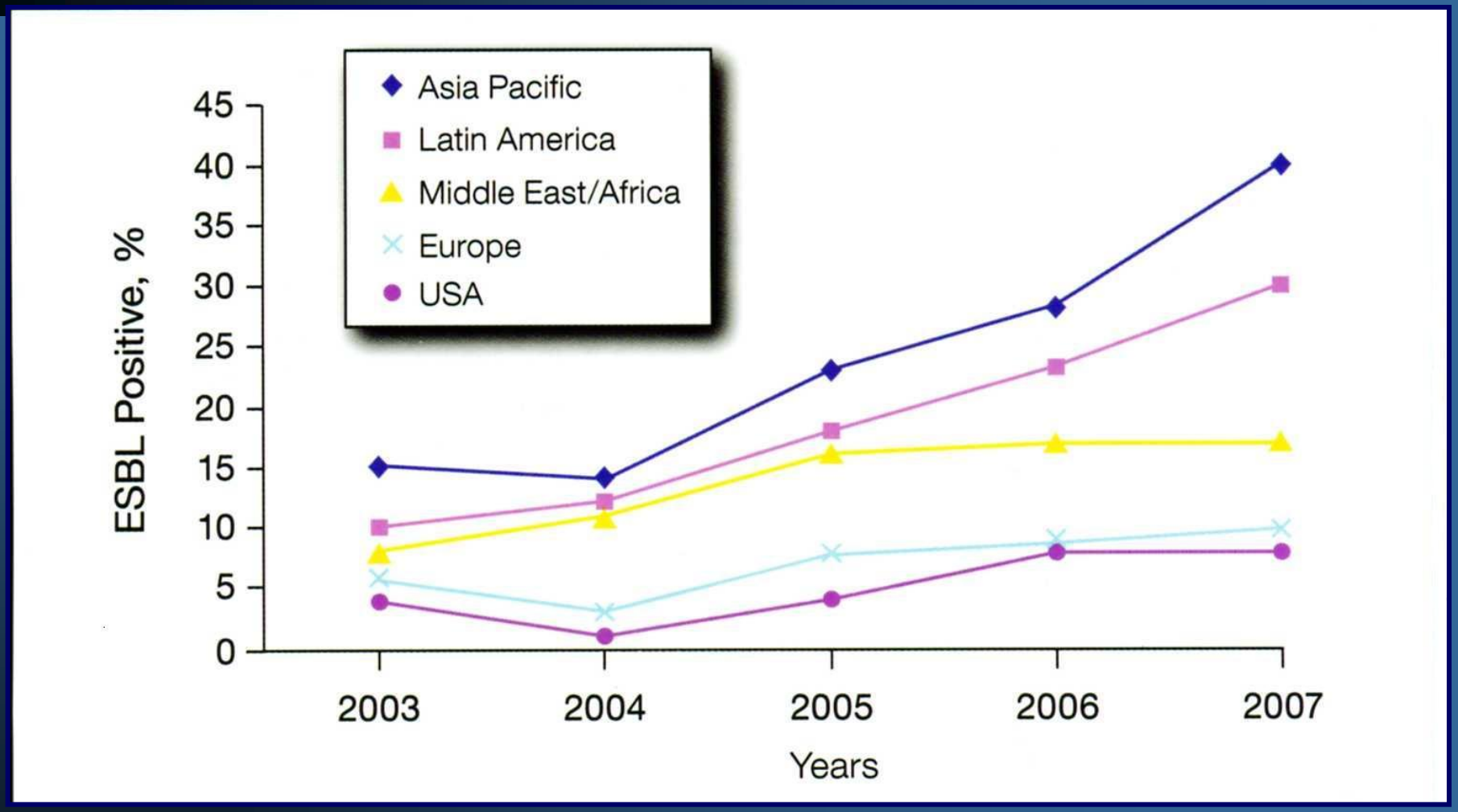


β-lattamasi ad ampio spettro

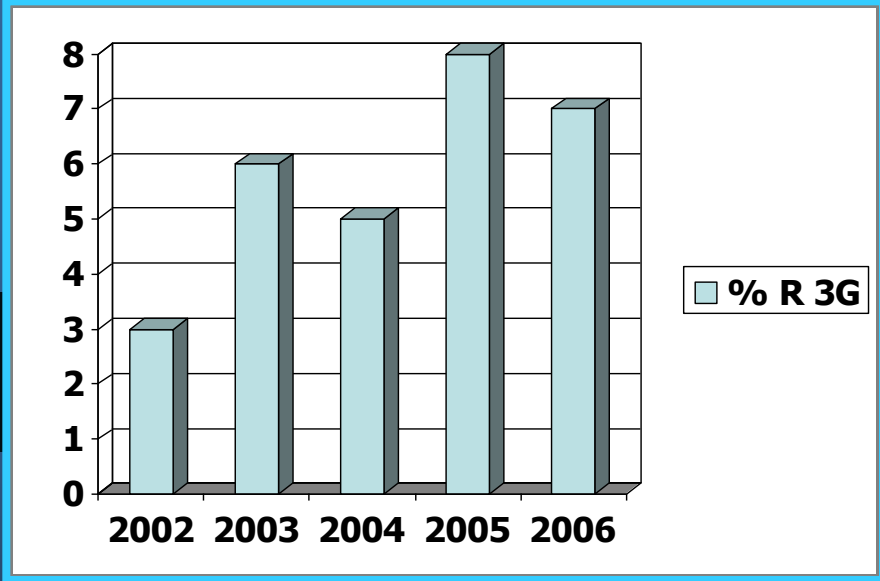
resistenza a:
penicilline
cefalosporine a spettro ristretto

β-lattamasi a spettro esteso

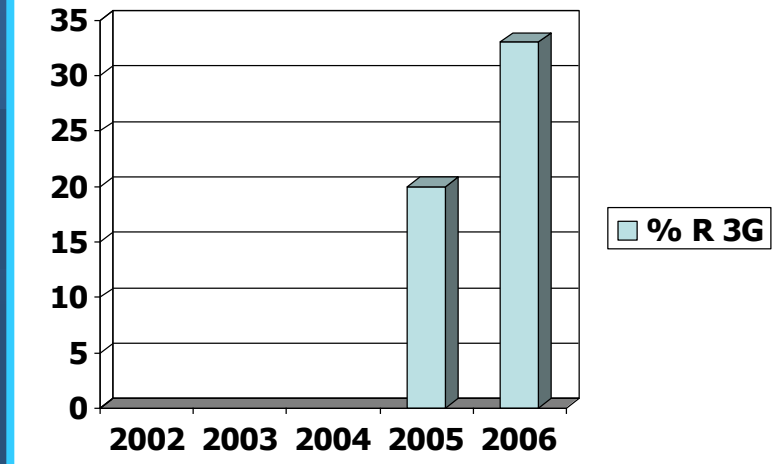
resistenza a:
penicilline
cefalosporine a spettro ristretto
cefalosporine a spettro esteso
monobattami

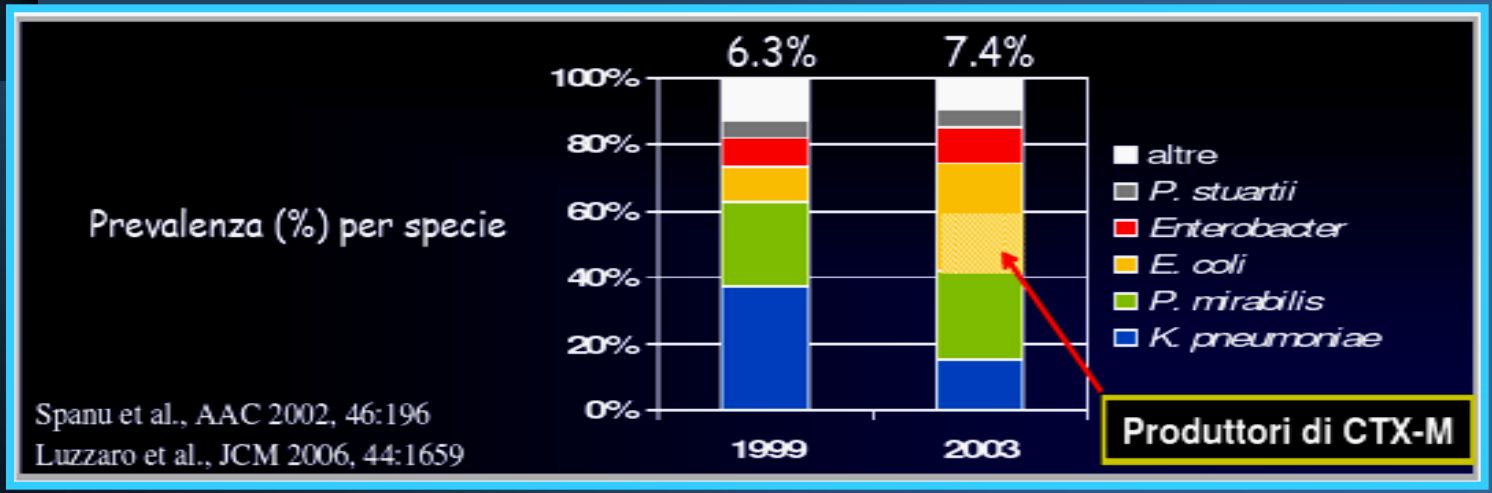

Asia Pacific
Latin America
Middle East/Africa
Europe
USA
ESBL Positive, %
45
40
35
30
25
20
15
10
5
0
2003
2004
2005
2006
2007
Years

Prevalenza di *E. coli* resistenti alle cefalosporine 3G

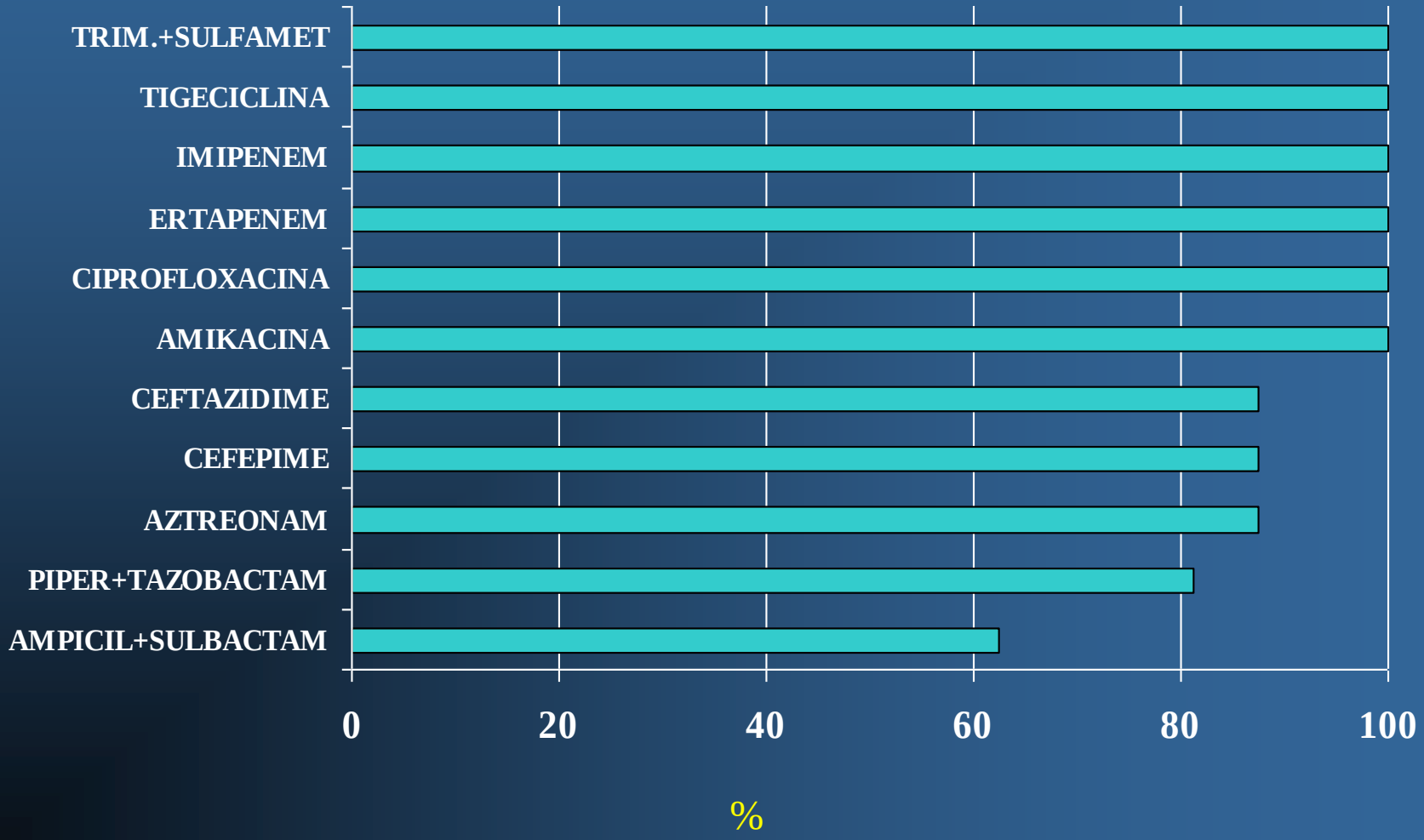


Prevalenza di *K.pneumoniae* resistenti alle cefalosporine 3G

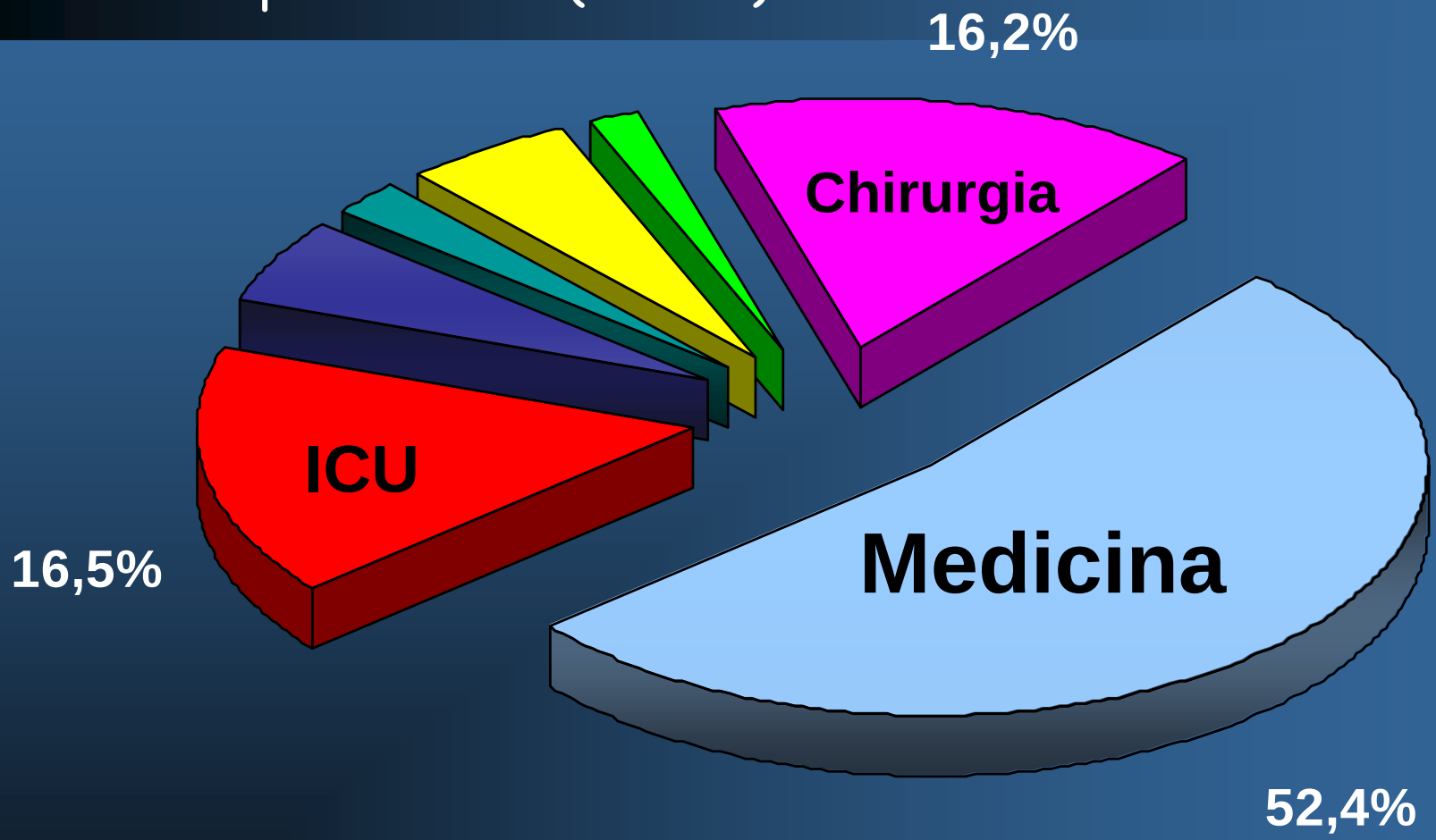




Sensibilità agli antibatterici degli isolati di *K. pneumoniae* da materiale del sito chirurgico, anno 2008



SORVEGLIANZA NAZIONALE 2003
Pazienti ospedalizzati (n=504)

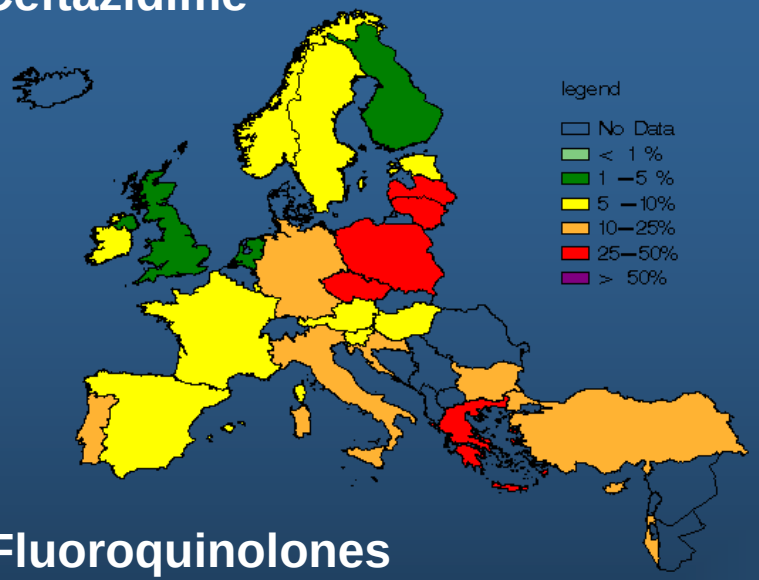


TERAPIA DELLE INFEZIONI DA ENTEROBATTERI PRODUTTORI DI ESBL

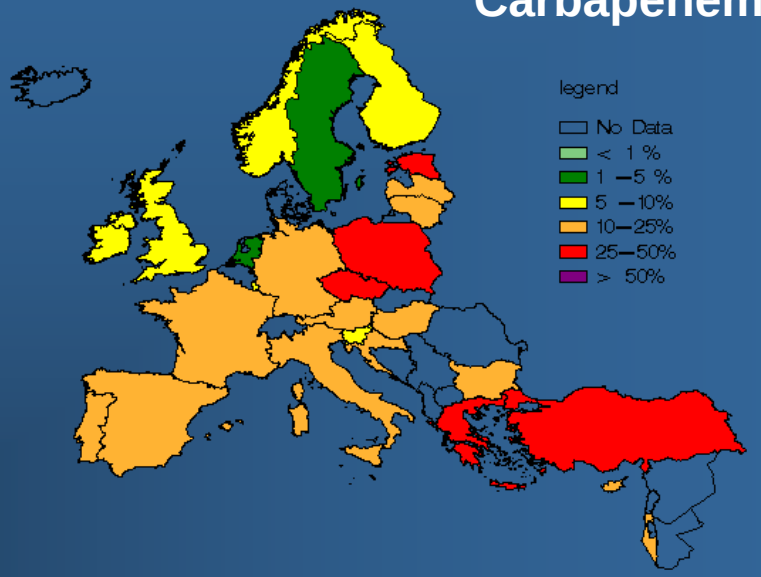
1	IMIPENEM	
	MEROPENEM	(ATTIVI SU TUTTI GLI ENTEROBATTERI ESBL +)
	ERTAPENEM	
2	TIGECICLINA	(NON ATTIVA SU PROTEUS)
3	COLIMICINA	(NON ATTIVA SU PROTEUS E SERRATIA)

P. aeruginosa – % invasive isolates resistant to:

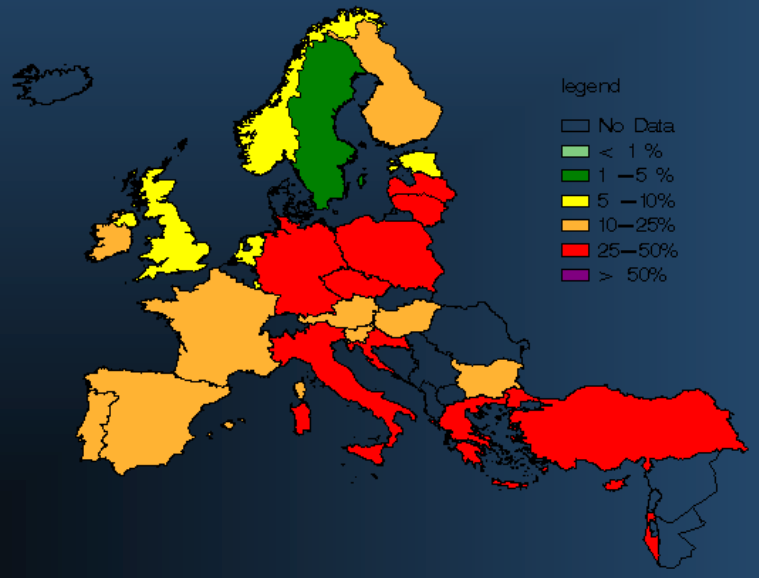
Ceftazidime



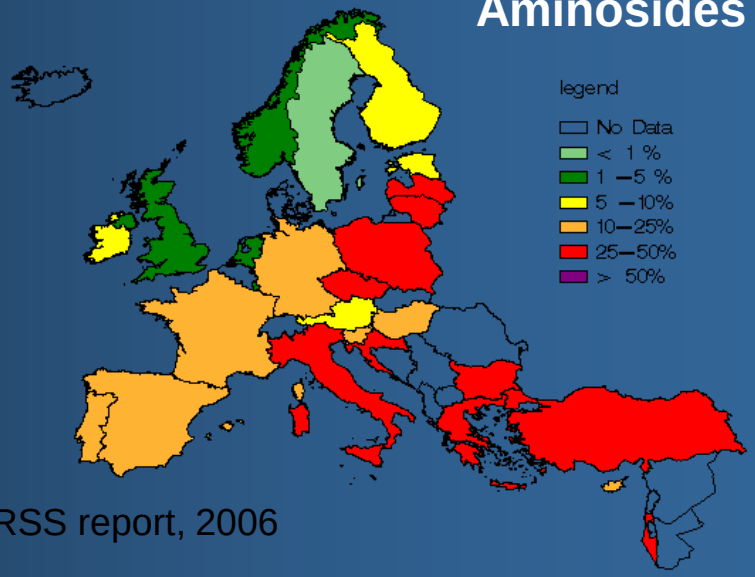
Carbapenems



Fluoroquinolones

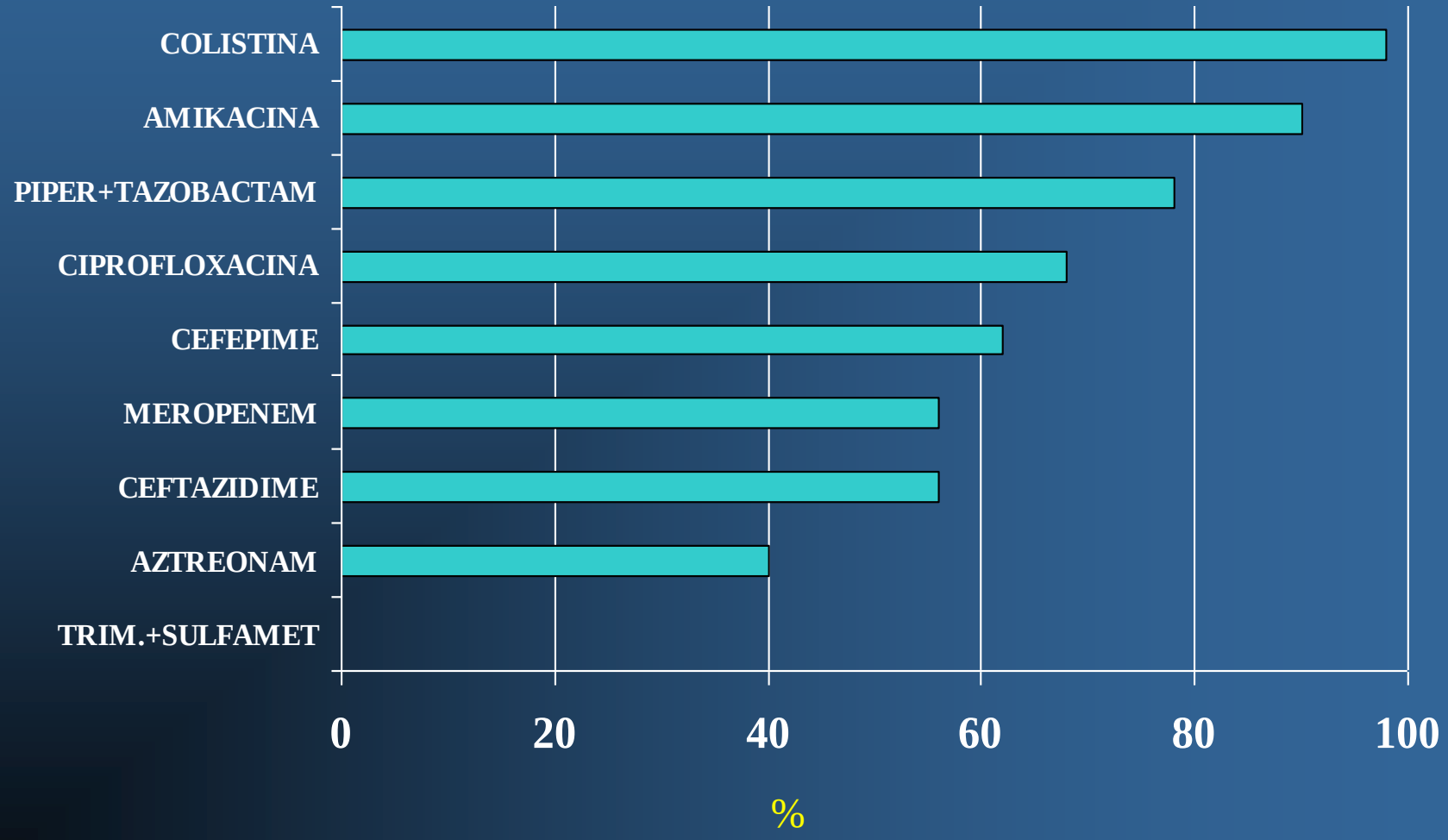


Aminosides

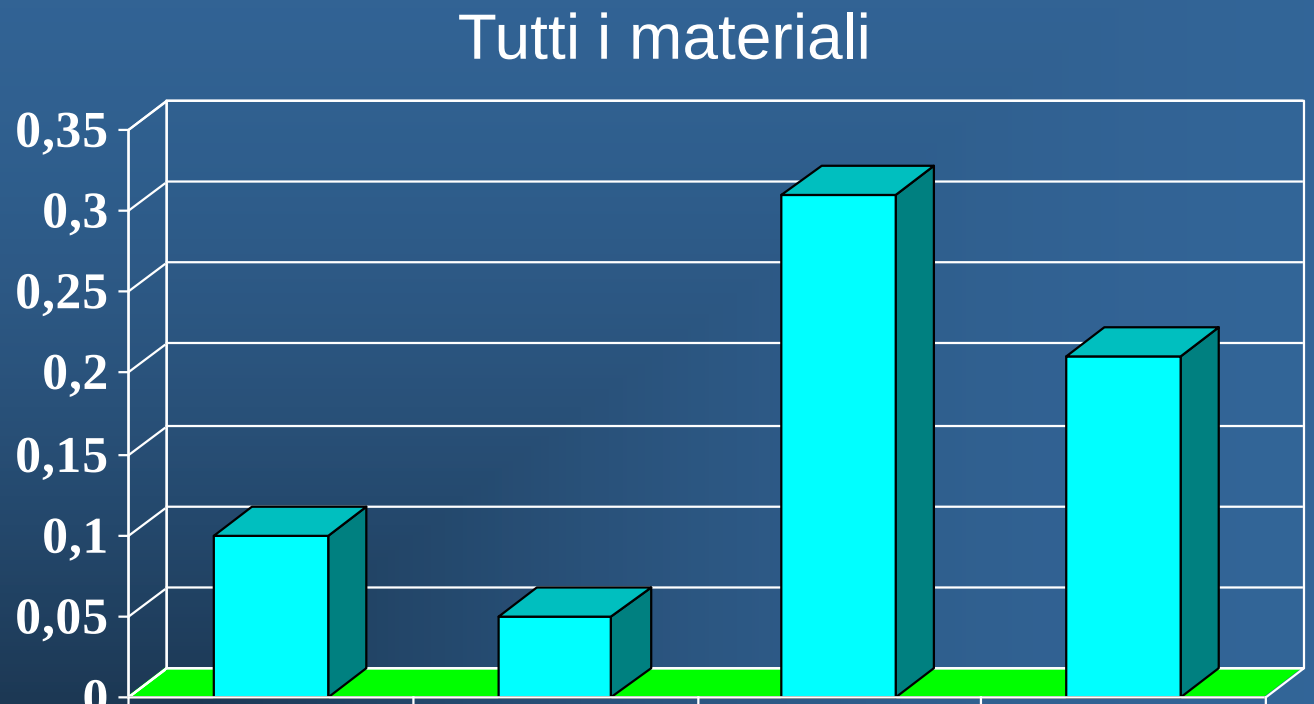


EARSS report, 2006

Sensibilità agli antibatterici degli isolati di *P. aeruginosa* da materiale del sito chirurgico anno 2008



P. aeruginosa multi-resistente*



	2005	2006	2007	2008
incidenza per 1000 giorni paziente	**0,1**	**0,05**	**0,31**	**0,21**

* Resistenza a ceftazidime, cefepime, piperacillina/tazobactam e carbapenemici

TERAPIA DELLE INFEZIONI DA PS. AERUGINOSA MULTI RESISTENTE

1. CEFTAZIDIME, CEFEPIME, AZTREONAM, IMIPENEM, MEROPENEM, PIPERACILLINA TAZOBACTAM

   +

   AMIKACINA o CIPROFLOXACINA o LEVOFLOXACINA

2. COLIMICINA

3. COLIMICINA + RIFAMPICINA

4. COLIMICINA + MEROPENEM

Terapia delle ferite infette postoperatorie

	Ia scelta	IIa scelta	
Chirurgia che non coinvolge il tratto G. I. o genitale femminile			**Se compaiono bacilli Gram neg aggiungere Amoxicillina Clavulanato o Ertapenem o Piperacillina Tazobactam**
senza sepsi	**Cotrimoxazolo**	**Clindamicina**	
con sepsi	**Vancomicina**	**Daptomicina Ceftobiprolo**	
Chirurgia che coinvolge il tratto G.I. o genitale femminile			
Infezioni gravi	**Piperacillina Tazobactam o Carbapenemi o Cefalosporine 3a + Metronidazolo + Vancomicina o Daptomicina**		
Infezioni di lieve entità	**Amoxiclavulanato ± Cotrimoxazolo**		

Sanford 2008

INFEZIONI DELLA PELLE E DEI TESSUTI MOLLI

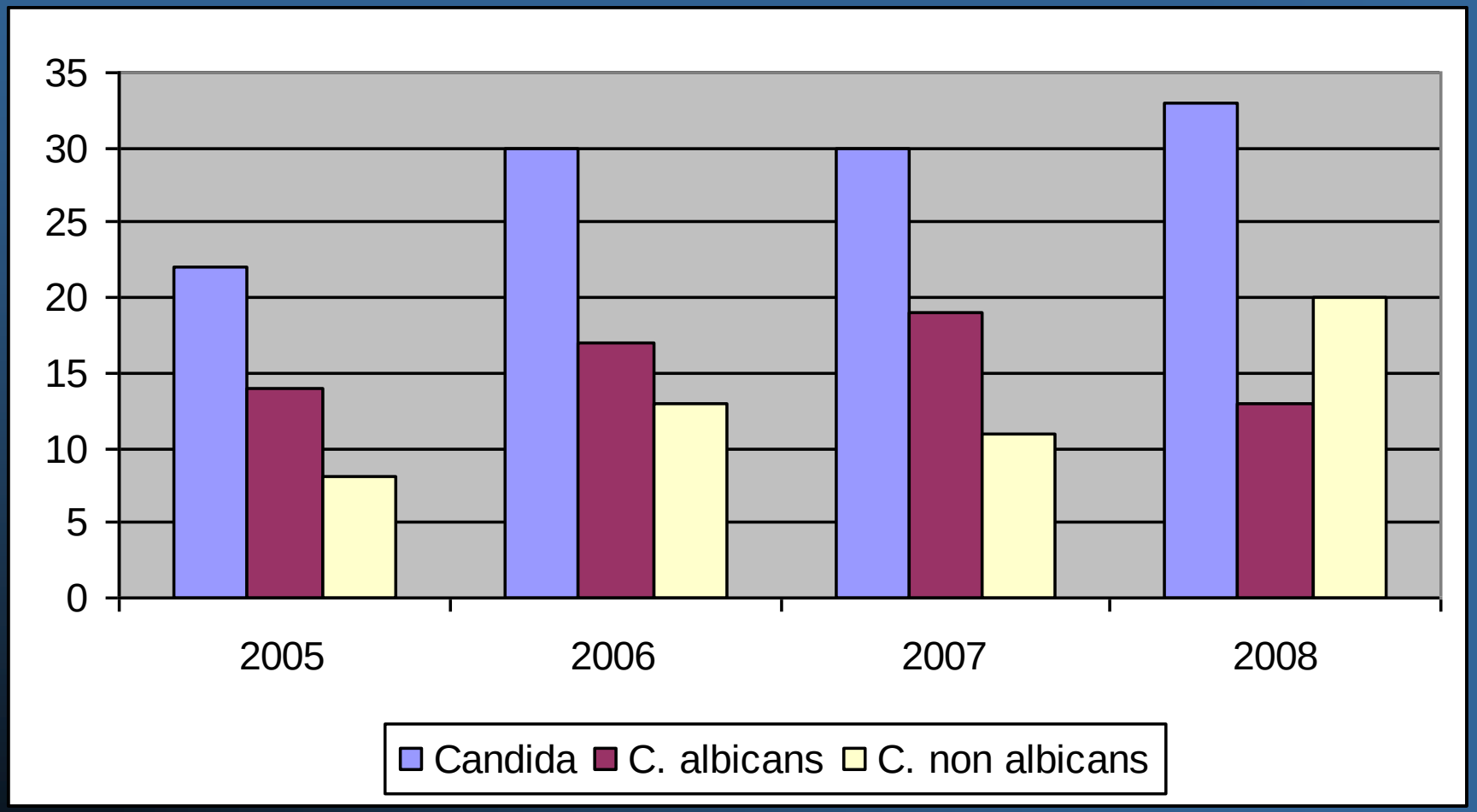
Ferita infetta postoperatoria	S. Aureo Enterobatteri	•Amoxicillina/Clavulanato •Cefalosporina+Fluorchinoloni •Glicopeptidi+Fluorchinoloni •Tigeciclina
Ferita infetta postoperatoria con sepsi	S. Aureo Enterobatteri	•Piperacillina/Tazobactam •Ampicillina/Sulbactam •Cefalosporina 3a } +/- glicopeptidi •Tigeciclina
Ferita infetta postoperatoria (chirurgia gastrointestinale)	S. Aureo Enterobatteri Anaerobi Enterococchi	•Piperacillina/Tazobactam+/- glicopeptidi •Imipenem/Meropenem /Ertapenem+/- glicopeptidi •Cefalosporine 3a + Metronidazolo+/- glicopepetidi •Tigeciclina

	COSTI DIE	
TEICOPLANINA 400 mg 6 mg/kg/die	6 mg/kg/die=420 mg 3 flac./die: **62.49€**	1 flac.=200 mg spreco: 18.75€
TEICOPLANINA 800 mg 12 mg/kg/die	12 mg/kg/die=840 mg 5 flac./die: **104.15€**	1 flac.=200 mg spreco: 16.66€
VANCOMICINA 2gr/die	4 flac./die: **7.68€**	1 flac.=500 mg
QUINUPRISTIN/DALFOPRISTIN 7,5 mg/kg x 3 die	7,5 mg/kg x 3 die=1.575 mg 4 flac./die: **209.92€**	1 flac.=500 mg spreco: 44.61€
LINEZOLID 600 mg ev x 2 die	2 sacche/die: **121.86€**	1 sacca=600 mg
LINEZOLID 600 mg os x 2 die	2 cpr/die: **121.9€**	1 cpr=600 mg
DAPTOMICINA 4 mg/kg/die	4 mg/kg/die=280 mg 1 flac./die: **79.04€**	1 flac=350 mg spreco: 15.81€
DAPTOMICINA 6 mg/kg/die	6 mg/kg/die=420 mg 2 flac./die: **158.08€**	1 flac=350 mg spreco: 63.23€
TIGECICLINA 100 mg per 50 mg ogni 12 ore die	2 flac./die: **104.72€**	1 flac.=50 mg

Candidemie OCM-Verona: Gennaio 2005 - Giugno 2008

Specie isolata 2005-2008	Unità di Terapia Intensiva (%)	Reparti Chirurgici (%)	Reparti medici (%)
C.albicans	28/54 (51.85 %)	16/30 (53.33 %)	9/16 (56.25 %)
C.parapsilosis	13/54 (24.07 %)	5/30 (16.67 %)	3/16 (18.75 %)
C.glabrata	4/54 (7.41 %)	3/30 (10.00%)	2/16 (12.50 %)
C.tropicalis	5/54 (9.26 %)	3/30 (10.00 %)	1/16 (6.25 %)
C.krusei	1/54 (1.85 %)	1/30 (3.33 %)	0/16 (0 %)
Altre NCAC	3/54 (5.56 %)	2/30 (6.67 %)	1/16 (6.25 %)
TOTALE	54/54 (100 %)	30/30 (100 %)	16/16 (100 %)

Numero isolati di Candida da materiali del sito chirurgico



Antimicotici - Consumo e spesa complessivo AO Verona - anni 2007 e 2008

Descrizione_Principio_Attivo	n° ddd 2007	n° ddd 2008	scost% n°ddd	spesa 2007	spesa 2008	scost% spesa
caspofungin	413	700	69,31%	180.362	303.438	68,24%
amfotericina B in complessi lipidici	*5.734*	*7.609*	*32,69%*	*182.295*	*242.394*	*32,97%*
amfotericina B liposomiale	*1.854*	*2.274*	*22,65%*	*190.547*	*233.706*	*22,65%*
amfotericina B	*1.644*	*1.201*	*-26,93%*	*6.664*	*4.846*	*-27,29%*
Totale amfotericina B	9.233	11.084	20,05%	379.506	480.946	26,73%
voriconazolo	1.158	1.373	18,57%	175.589	192.302	9,52%
fluconazolo	23.585	21.739	-7,82%	217.696	180.025	-17,30%
posaconazolo	58	908	1472,73%	7.668	120.603	1472,74%
itraconazolo	8.965	3.631	-59,50%	17.585	3.768	-78,57%
ketoconazolo	100	1.150	1050,00%	48	1.151	2321,43%
flucitosina	25	30	19,00%	878	1.014	15,45%
Totale complessivo	**43.536**	**40.615**	**-6,71%**	**979.333**	**1.283.248**	**31,03%**

What is the treatment of candidemia in non-neutropenic patients?

1. If *Candida* species is unknown, either fluconazole (800mg loading dose, 400 mg daily) or an echinocandin is appropriate initial therapy for most adult patients (AI)
2. An **echinocandin** is favored for patients with
   a.) moderately severe to severe illness, **or**
   b.) among patients who have had recent azole exposure for either treatment or prophylaxis (AIII).
3. **Fluconazole** is recommended among patients who are
   a) less critically ill **and**
   b).who have no recent azole exposure (AIII).
4. Transition from an echinocandin to fluconazole for pts with isolates likely to be susceptible to fluconazole (eg, *C.albicans*) and who are clinically stable. (AIII).

What is the treatment of candidemia in non-neutropenic patients?

5. Among patients with proven or suspected infection due to *C. glabrata,* an echinocandin is preferred as initial therapy (BIII). Transition to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility (BIII). For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow up cultures are negative, continuing an azole to completion of therapy is reasonable (BIII).

What is the treatment of candidemia in non-neutropenic patients?

6. Among patients with proven or suspected infection due to *C. parapsilosis* or fluconazole is preferred as initial therapy (BIII). Among pts already receiving an echinocandin and who are clinically stable, OK to continue.

7. **In resource-limited environments or where echinocandins are unavailable, amphotericin B is an effective alternative to an echinocandin** (AI). Transition from amphotericin B to fluconazole is recommended Among patients who are clinically stable and have an isolate with predictable susceptibility to fluconazole (AI).

What is the treatment of candidemia in non-neutropenic patients?

8. Voriconazole is an effective treatment for candidemia, but it offers little advantage over fluconazole as primary therapy for candidemia. Its role is generally limited to transitional oral therapy for selected cases of invasive candidiasis (eg *C. krusei*) (BIII).
9. Intravenous catheter removal is recommended for non-neutropenic patients with candidemia (AII).
10. Recommended duration of therapy for candidemia without persistent fungemia or metastatic complications is for 2 wks following documented clearance of *Candida* from the bloodstream *and* resolution of symptoms attributable to candidemia (AI)