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Il Manuale di Terapia Antibiotica Empirica: Il Punto di Vista dell'Infettivologo

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Insegnamenti Tradizionali

- **Definire** la diagnosi
- **Scegliere** l'antibiotico
- **Definire** dosaggio e durata della terapia
- **Prevenire** gli effetti collaterali
- **Ridurre** la comparsa di antibiotico-resistenza

Appropriatezza

Stewardship Applicazioni

Etiologia

- **MRSA**
- **VRE**
- **ESBL**
- **KPC**
- **R-FQ**

Diagnosi

- CAP
- HCAP
- HAP / VAP
- EI / BSI
- Tbc
- ….

Reparto

- **Chirurgia**
  - **Profilassi**
  - **Terapia**
- **Medicina Interna & DEA**
- **Terapia Intensiva**
- **Oncoematologia**

Molecole / Consumo

- Vancomicina, Carbapenemi, Fluorochinoloni
- Daptomicina, Linezolid, Pip/tazo,
- Antifungini……

Redefining ESKAPE…as ESCAPE

Proposed revisions capture additional pathogens

E	*Enterococcus faecium*	
S	*Staphylococcus aureus*	
C	*Clostridium difficile*	→ *Acknowledges the growing virulence of C. difficile*
A	*Acinetobacter baumannii*	
P	*Pseudomonas aeruginosa*	
E	Enterobacteriaceae	→ *Enterobacteriaceae captures K. pneumoniae, Enterobacter spp., and other resistant species including Escherichia coli and Proteus spp.*

Peterson LR. *Clin Infect Dis.* 2009;49:992.

Acinetobacter:
An Old Friend, but a New Enemy

Towner, KJ. J Hosp Infection 2009; 73: 355-63

1. **MDR strains**
   - Primarily in hospitals during outbreaks
   - *A. baumannii* and its close relatives
2. **Sensitive strains**
   - Colonizing 20-70% of individuals & animals
   - Part of the spoilage flora of different foodstuffs
   - *A. johnsonii, A. lwoffii, A. radioresistens*
3. **Sensitive strains**
   - Isolated in the environment, soil or wastewaters
   - *A. calcoloaceticus, A. johnsonii*

Bacteremia by ESBL

De Rosa FG et al Infection 2011

Mortality at 21 days was 15% Vs. 35% with appropriate or inappropriate treatment (p=0.05)

Previous positive blood cultures (p=0.004)
Septic shock (p=0.006)

Table 1 Antimicro
susceptibility test re
bloodstream isolate
producing *E. coli*, *K. pneumoniae* and *P.*

Meropenem	80 (100)	27 (94.6)	20 (100)
Piperacillin–tazobactam	47 (58.8)	15 (53.6)	18 (90.0)
Trimethoprim–sulfamethoxazole	32 (40.0)	14 (50.0)	7 (35.0)

Bacteremia by ESBL

De Rosa FG et al Infection 2011

Table 2 Characteristics of the 128 patients with bloodstream infection by ESBL-producing organisms

Variable	All patients ($n = 128$)	*E. coli* ($n = 80$)	*K. pneumoniae* ($n = 28$)	*P. mirabilis* ($n = 20$)
Patient related				
Males	90 (70.3)	58 (72.5)	18 (64.3)	14 (70.0)
Mean age in years ± SD	63.5 ± 17.4	64.1 ± 16.0	56.1 ± 21.4	71.7 ± 12.4
Ward				
Medical	71 (55.5)	42 (52.5)	14 (50.0)	15 (75.0)
Surgical	35 (27.3)	21 (26.3)	10 (35.7)	4 (20.0)
ICU	8 (6.3)	4 (5.0)	3 (10.7)	1 (5.0)
Hematology	14 (10.9)	13 (16.3)	1 (3.6)	0
OLT	9 (7.0)	8 (10.0)	1 (5.0)	0
Mean Charlson score ± SD	3.0 ± 2.1	3.2 ± 2.2	2.3 ± 1.9	2.8 ± 2.0
Sepsis or septic shock	16 (12.5)	11 (13.8)	1 (3.6)	3 (15.0)
Mean days between admission and diagnosis ± SD	18.3 ± 27.8	13.1 ± 18.2	37.8 ± 43.5	11.7 ± 19.8
Infection related				
CA	14 (11.0)	12 (15.0)	1 (3.6)	1 (5.0)
HC	57 (44.5)	36 (45.0)	7 (25.0)	14 (70.0)
HA	71 (55.5)	32 (40.0)	20 (71.4)	5 (25.0)
Source of infection				
Unknown	61 (47.1)	35 (43.8)	16 (57.1)	10 (50.0)
Urinary tract	12 (9.4)	7 (8.8)	1 (3.6)	4 (20.0)
Pancreatico-biliary tract	27 (22.0)	23 (28.8)	3 (10.7)	1 (5.0)
Abdominal tract	28 (21.9)	15 (18.8)	8 (28.6)	5 (25.0)

ICU intensive care unit, *OLT* orthotopic liver transplant, *CA* community-acquired, *HC* health-care associated, *HA* hospital-acquired

Bacteremia by ESBL

De Rosa FG et al Infection 2011

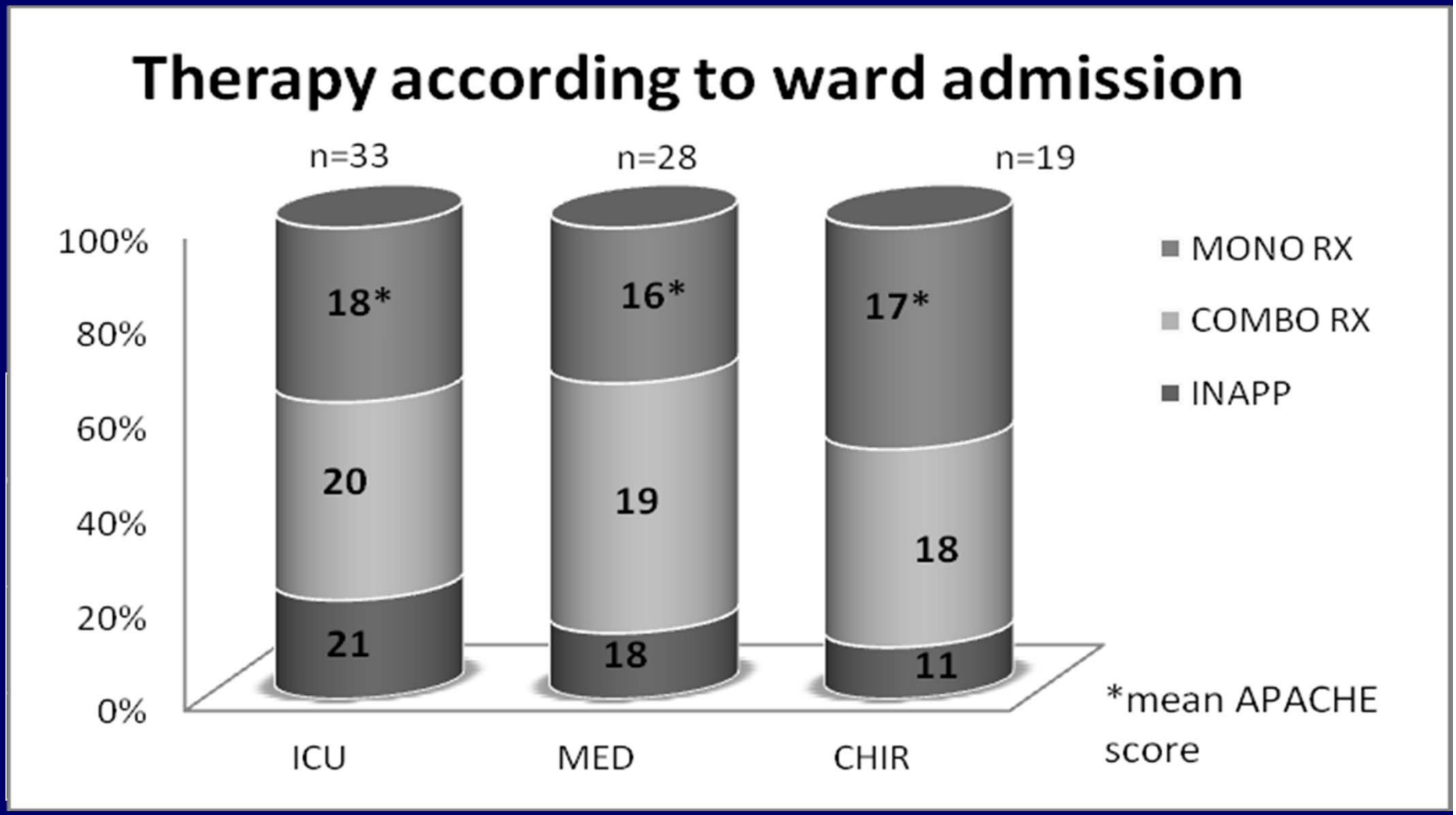
Amongst Patients Appropriately Treated,
40% had bacteremia diagnosed within five days by the hospital admission

Table 4 M
infection b
antimicrobi

Appropriate agents		
Carbapener		
Aminoglycosides	0	5
Fluoroquinolones	1 (16.6)	5
β-Lactam-β-lactamase inhibitors	2 (25)	6
Trimethoprim–sulphamethoxazole	0	1

(%) refers to the total number of patients treated with one class of antibiotics

KPC – BSI Torino
80 pazienti



S. aureus Bacteremia: Opening Pandora's Box

Chu et al Clin Infect Dis 2012

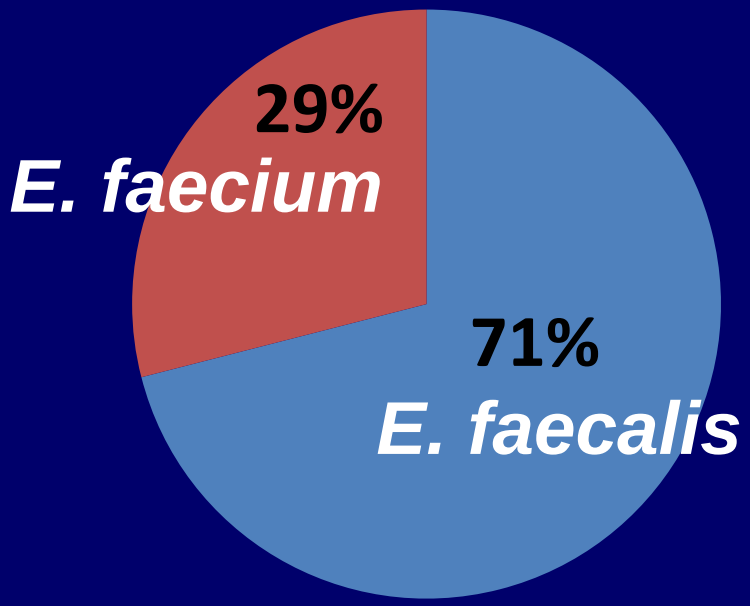
- As soon as the conversation begins, troubles related to incorrect information, misstated facts and other misunderstandings "fly out"
- Too-often such discussions include preliminary, second-hand, incomplete or incorrect information. Surprisingly, the impact of telephone consultations on patient outcomes has received little scientific scrutiny

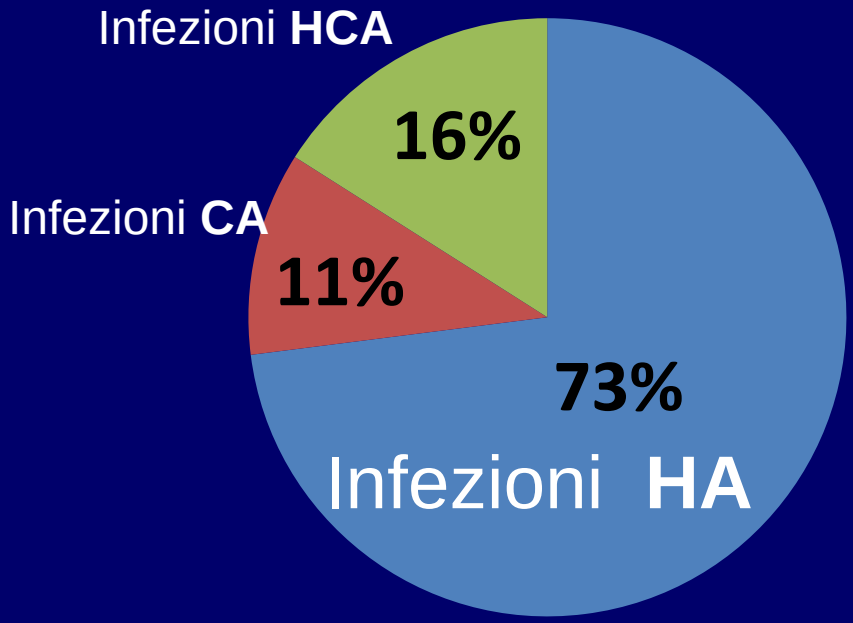
S. aureus Bacteremia & Infectious Diseases Consultation

Forsblom E et al Clin Infect Dis 2012

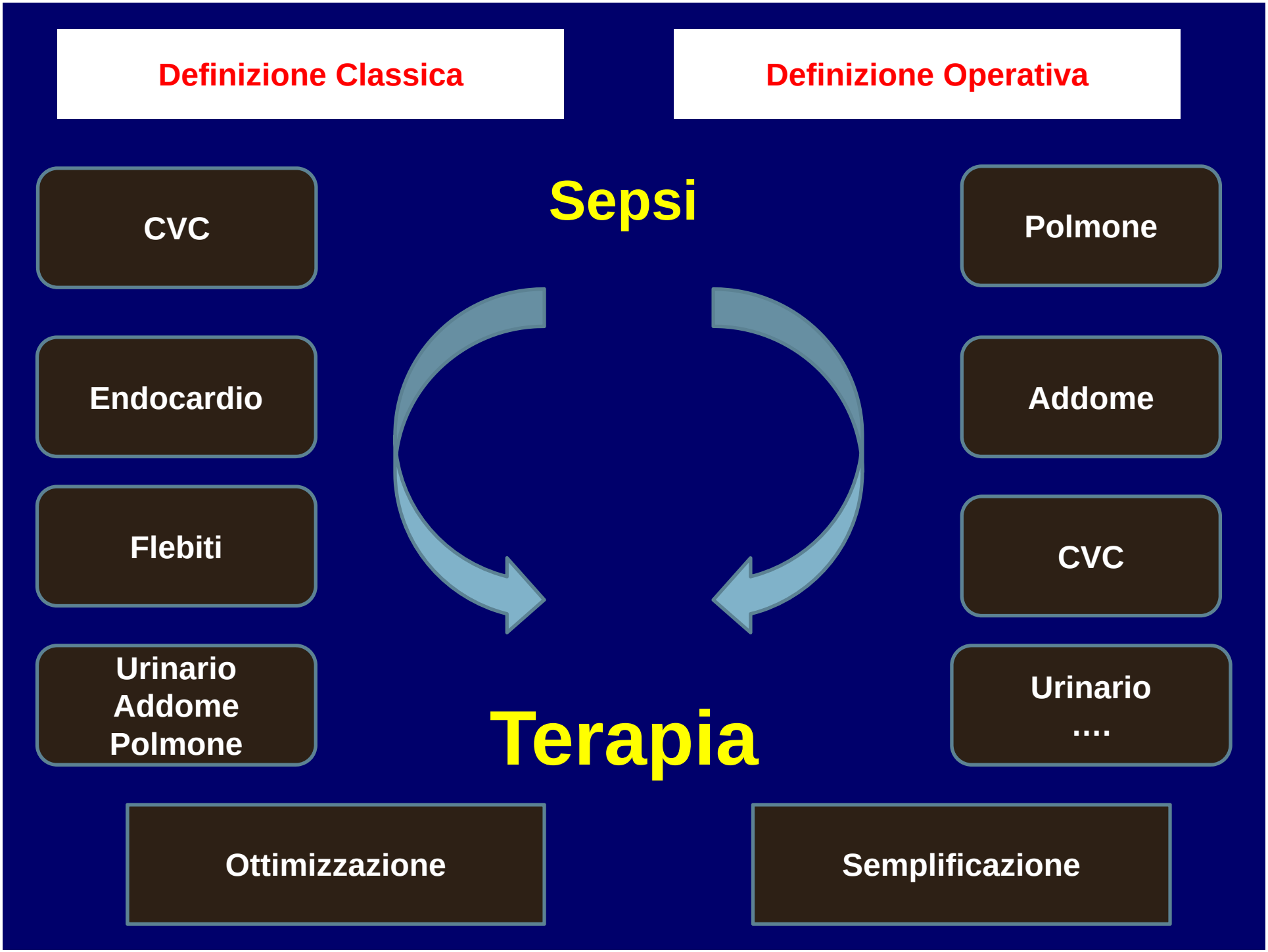
	Bedside consultation [1] n = 245 (%)	Telephone consultation [1] n = 62 (%)	No consultation n = 35 (%)	Bedside vs. telephone consultation OR (95% CI)	p	Bedside vs. no consultation OR (95% CI)	p
Male sex	160 (66)	38 (61)	21 (60)	1.19 (0.67 – 2.11)	0.56	1.26 (0.61 – 2.59)	0.54
Age (mean years ± SD)	53.2 ± 17.7	54.8 ± 16.5	55.2 ± 16.6	2.48 (3.32 – 6.45)	0.53	3.17 (4.29 – 8.21)	0.54
Healthcare-associated bacteraemia	141 (57)	31 (50)	22 (63)	1.36 (0.78 – 2.37)	0.29	0.80 (0.39 – 1.66)	0.55
Underlying disease classification [A]							
Healthy or nonfatal	174 (71)	36 (58)	17 (49)	1.77 (0.99 – 3.15)	0.05	2.59 (1.27 – 5.32)	0.008
Ultimately or rapidly fatal	71 (29)	26 (42)	18 (51)	0.57 (0.32 – 1.00)	0.05	0.39 (0.19 – 0.79)	0.008
Underlying conditions							
Diabetes	30 (12)	8 (13)	8 (23)	0.94 (0.41 – 2.17)	0.89	0.47 (0.19 – 1.13)	0.09
Coronary artery disease	47 (19)	13 (21)	10 (29)	0.89 (0.45 – 1.78)	0.75	0.59 (0.27 – 1.32)	0.19
Chronic lung disease	33 (14)	12 (19)	4 (11)	0.65 (0.31 – 1.35)	0.24	1.21 (0.40 – 3.64)	
Dialysis	31 (13)	6 (10)	4 (11)	1.35 (0.54 – 3.40)	0.52	1.12 (0.37 – 3.39)	0.84
Corticosteroid therapy [B]	12 (5)	3 (5)	2 (6)	1.01 (0.28 – 3.72)	0.98	0.85 (0.18 – 3.98)	0.84
Previous surgery [C]	59 (24)	14 (23)	11 (31)	1.09 (0.56 – 2.11)	0.80	0.69 (0.32 – 1.49)	0.35
Treatment related factors							
Severe sepsis [D]	16 (7)	6 (10)	11 (31)	0.65 (0.24 – 1.74)	0.39	0.15 (0.06 – 0.37)	< 0.0001
Intensive care unit, within 3 days	52 (21)	21 (34)	7 (20)	0.53 (0.29 – 0.97)	0.037	0.85 (0.34 – 2.09)	0.72
Intensive care unit, within 7 days	71 (29)	23 (37)	11 (31)	0.69 (0.39 – 1.24)	0.22	0.85 (0.39 – 1.84)	0.69
Hospitalization, days ± SD	38.7 ± 21.7	30.6 ± 23.0	24.9 ± 24.8	3.27 (1.69 – 14.5)	0.014	4.11 (5.73 – 21.9)	0.001
Time to defervescence, days ± SD	6.7 ± 9.7	12.6 ± 13.4	13.4 ± 14.7	1.67 (2.54 – 9.12)	0.001	2.19 (2.33 – 10.9)	0.003
Radiology [E]							
Transthoracic echocardiography	188 (77)	44 (71)	9 (26)	1.35 (0.72 – 2.52)	0.35	9.53 (4.22 – 21.5)	< 0.0001
Transesophageal echocardiography	27 (11)	2 (3)	1 (3)	3.73 (0.86 – 16.1)	0.06	4.23 (0.56 – 32.1)	0.13
Whole-body computed tomography	167 (68)	34 (55)	10 (29)	1.76 (0.99 – 3.11)	0.049	5.35 (2.45 – 11.7)	< 0.0001
Leucocyte Indium-111-scintigraphy	105 (43)	8 (13)	3 (9)	5.06 (2.31 – 11.1)	< 0.0001	8.00 (2.39 – 26.8)	< 0.0001
Infection foci							
Any deep infection focus	191 (78)	33 (53)	10 (29)	3.11 (1.74 – 5.57)	< 0.0001	8.84 (4.00 – 19.5)	< 0.0001
Osteomyelitis	78 (32)	6 (10)	1 (3)	4.36 (1.80 – 10.6)	< 0.0001	15.9 (2.14 - 118)	< 0.0001
Deep-seated abscesses	110 (45)	10 (16)	0	4.24 (2.06 – 8.72)	< 0.0001	---	---
Endocarditis	39 (16)	4 (7)	1 (3)	2.75 (0.94 – 7.99)	0.055	6.44 (0.86 – 48.4)	0.039
Skin or soft tissue infection	174 (71)	32 (52)	14 (40)	2.29 (1.30 – 4.06)	0.004	3.68 (1.77 – 7.63)	< 0.0001
Proper antibiotic therapy	208 (85)	39 (63)	16 (54)	2.78 (1.28 – 6.05)	0.008	3.96 (1.47 – 10.6)	0.004
Mortality							
Within 3 days	1 (0.5)	1 (2)	9 (26)	0.25 (0.02 – 4.05)	0.29	0.01 (0.00 – 0.09)	< 0.0001
Within 7 days	2 (1)	5 (8)	9 (26)	0.09 (0.02 – 0.49)	0.001	0.02 (0.01 – 0.12)	< 0.0001
Within 28 days	12 (5)	10 (16)	12 (34)	0.27 (0.11 – 0.65)	0.002	0.09 (0.04 – 0.25)	< 0.0001
Within 90 days	23 (9)	18 (29)	16 (46)	0.25 (0.13 – 0.51)	< 0.0001	0.12 (0.06 – 0.27)	< 0.0001
Relapse of bacteraemia	3 (1)	1 (2)	2 (6)	0.76 (0.08 – 7.39)	0.81	0.21 (0.03 – 1.27)	0.061

278 Sepsi Enterococciche: 2008-2011





MORTALITA' A FINE RICOVERO: **25%**


Definizione Classica
Definizione Operativa
Sepsi
CVC
Endocardio
Flebiti
Urinario
Addome
Polmone
Polmone
Addome
CVC
Urinario
....
Terapia
Ottimizzazione
Semplificazione

Terapia & Strategie Terapeutiche

Terapia

- S. aureus
- Stafilococchi coagulasi-negativi
- Enterococchi
- Gram-negativi ESBL
- KPC
- *Candida spp.*

Strategia Terapeutica

- Sepsi «precoci»
- Carbapenemi
- Terapia empirica delle endocarditi
- Daptomicina
- Rifampicina
- Aminoglucosidi

Device Endovascolari

- Aumento sproporzionato di infezioni/EI su device
- Marcato aumento degli impianti
- Cambiamento dei materiali e complessità dei device
- **ICE: 6.7%**
- **RIEI 11.9%**

Baddour LM. Circulation 2010; 121:458-477.

Uno Sguardo alla Clinica
Dati da RIEI

Febbre > 38°C	62,50%
Noduli di Osler	3,80%
Macchie di Roth	0
Lesioni di Janeway	0,80%
Evento embolico vascolare	8,30%
Splenomegalia	15,35%
Dentatura mediocre	50,15%
Nuovo soffio	36,32%
Peggioramento di soffio noto	16,60%
Peggioramento di soffio NON noto	24,56%
Scompenso cardiaco	44,3 %, sinistro nel 68,4% dei casi
Scompenso severo NYHA 3 o 4	22,20%
Stato infiammatorio	89%
Aumento VES	63,68%
Edema polmonare	8,53%

RIEI 2013

	Sede delle EI (ecocardio)									
	Device endcavitario		Protesi valvolari		Valvola Nativa		Altro		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Stafilococco aureo	18	36.73	15	16.3	93	28.7	7	25.93	133	27.03
Stafilococco epidermis	10	20.41	21	22.83	26	8.02	4	14.81	61	12.4
Stafilcocco coagulasi neg	5	10.2	7	7.61	27	8.33	5	18.52	44	8.94
Streptococco bovis	0	0	6	6.52	48	14.81	3	11.11	57	11.59
Streptococco viridans	0	0	9	9.78	61	18.83	3	11.11	73	14.84
Stafilococco lugdunensis	0	0	0	0	2	0.62	1	3.7	3	0.61
Enterococco faecalis	10	20.41	22	23.91	35	10.8	3	11.11	70	14.23
Hacek	1	2.04	0	0	3	0.93	2	7.41	6	1.22
Enterococco faecium	0	0	3	3.26	2	0.62	0	0	5	1.02
Escherichia coli	0	0	3	3.26	6	1.85	2	7.41	11	2.24
Klebsiella	1	2.04	1	1.09	2	0.62	0	0	4	0.81
Pseudomonas	0	0	1	1.09	3	0.93	0	0	4	0.81
Total	49	100	92	100	324	100	27	100	492	100

RIEI 2013

	Sede delle EI (ecocardio)								Total	
	Device endcavitario		Protesi valvolari		Valvola Nativa		Altro		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Genere										
Femmina	21	22.58	42	36.84	112	25.69	10	29.41	185	27.33
Maschio	72	77.42	72	63.16	324	74.31	24	70.59	492	72.67
Età										
<=40	4	4.3	5	4.39	68	15.6	3	8.82	80	11.82
41-50	7	7.53	8	7.02	73	16.74	4	11.76	92	13.59
51/60	10	10.75	8	7.02	73	16.74	4	11.76	95	14.03
61-70	26	27.96	28	24.56	92	21.1	11	32.35	157	23.19
71-80	33	35.48	51	44.74	100	22.94	9	26.47	193	28.51
>80	13	13.98	14	12.28	30	6.88	3	8.82	60	8.86

Nostro Modello

- Non restrittivo *ab initio*
- Multidisciplinare
  - Infection control
  - Pharmacy
  - Microbiology & Infectious Diseases
- Meropenem & ciprofloxacina
- Isolamento
- Profilassi in Chirurgia
- Prontuario terapeutico di riferimento

Appropriatezza

Start Smart – Then Focus

Ashiru-Oredrope D et al JAC 2012; 67 (S1): i51-i63

- **Evidence-based optimal standards**
  - for routine antimicrobial use
- **Ensuring competence & educational programmes**
  - for all staff that use antimicrobials
- **Communicating**
  - antimicrobial issues to all stakeholders
- **Auditing**
  - the impact and uptake of these processes
- **Optimizing**
  - outcomes for patients who receive antimicrobials

Start Smart – Then Focus

Ashiru-Oredrope D et al JAC 2012; 67 (S1): i51-i63

- **Improved cost-effectiveness of antimicrobial therapy**
  - **Directly**
    - **Limiting the excess and inappropriate use**
    - **Pmpting active iv-to-po switch therapy**
  - **Indirectly**
    - **Reducing the risk of drug-related adverse events & associated costs**
    - **Promoting optimized and timely delivery of antimicrobials & thus reducing unwanted consequences such as sub-therapeutic dosing and treatment failure**

Richiami alla Farmacia & alla Farmacologia