associazione microbiologi clinici italiani

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Palacongressi di Rimini

CORSO PRE-CONGRESSUALE AMCLI 2017

EPIDEMIOLOGIA E RUOLO CLINICO DI MRSA: UN QUADRO IN CONTINUA EVOLUZIONE

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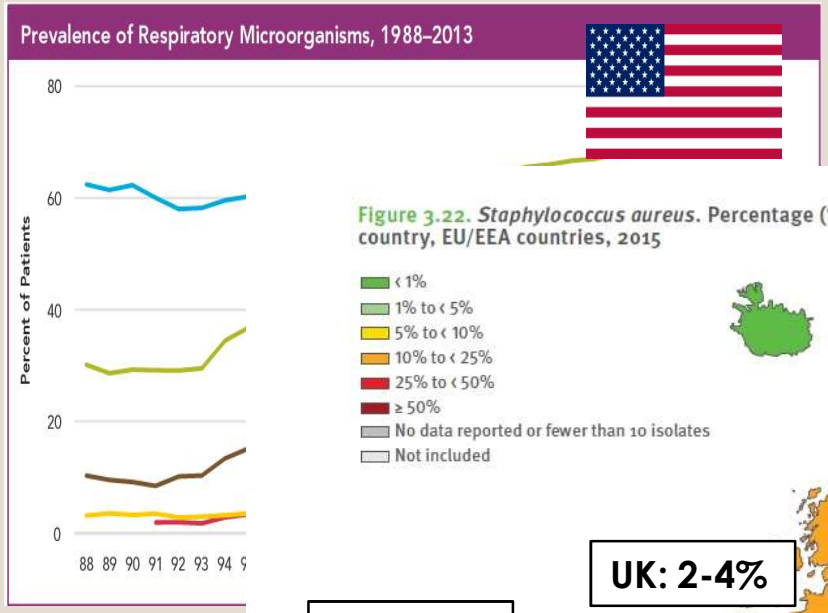
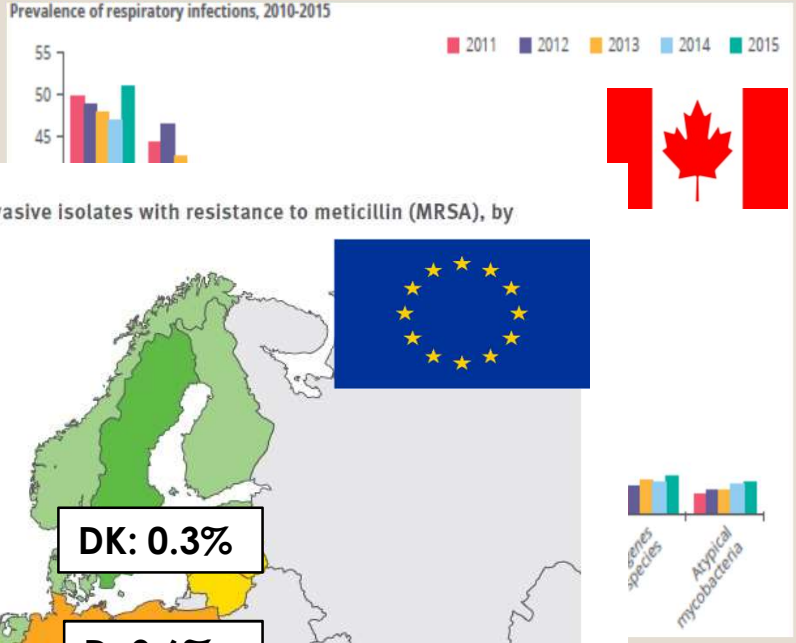
Prevalenza di MRSA

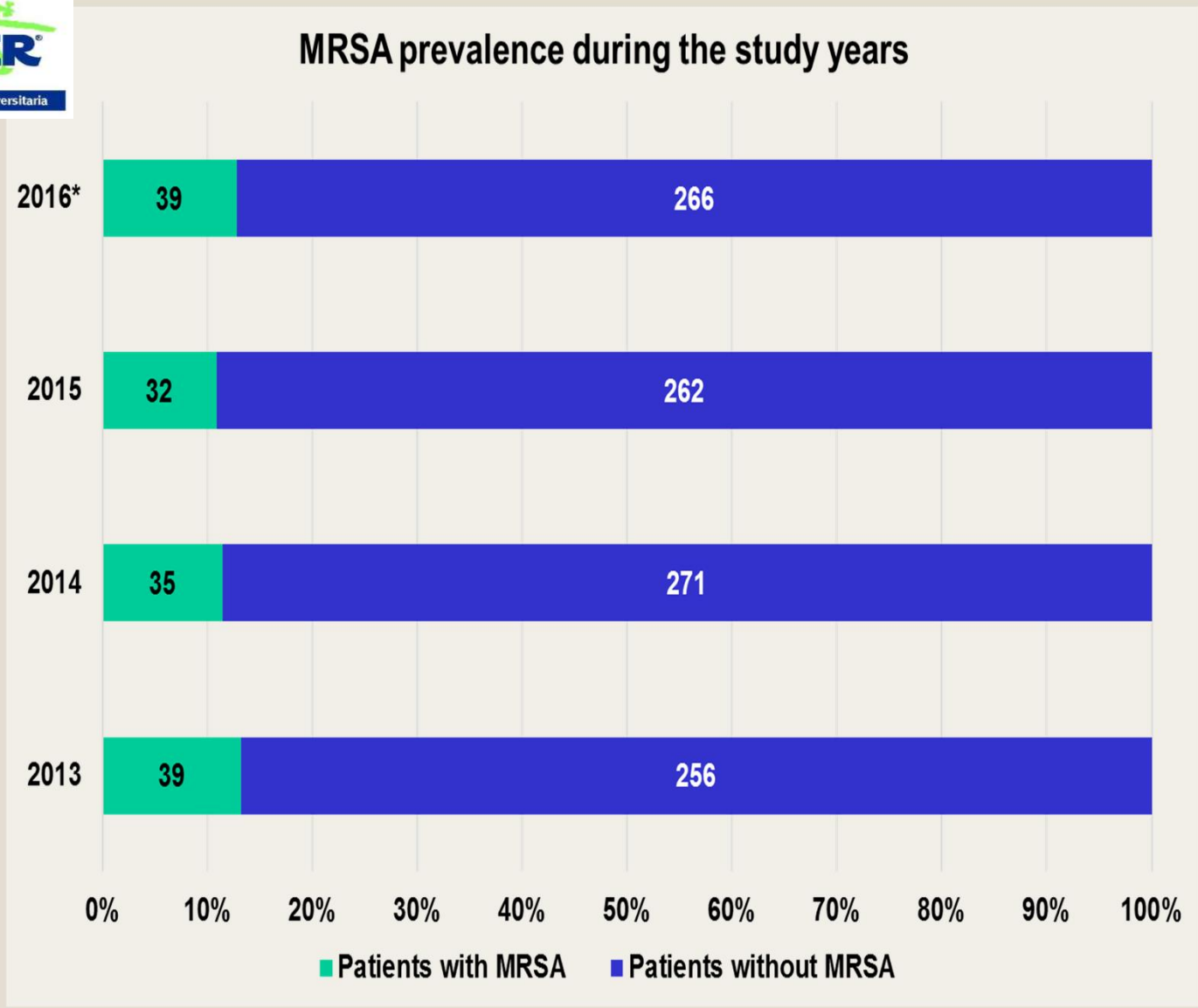


NACFC regis



3 Annual Report

MRSA IN FC

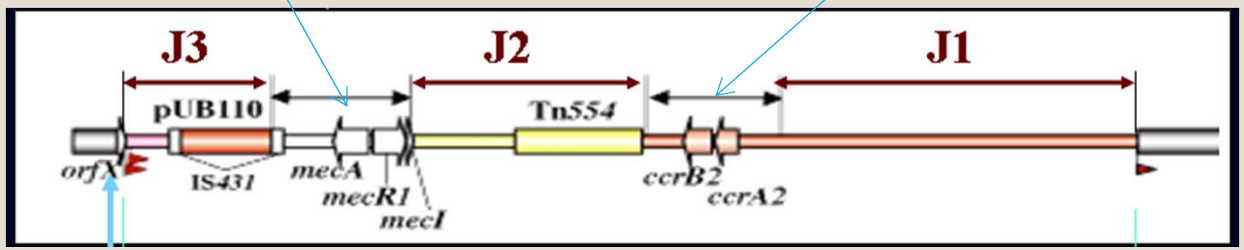


Dati centro FC Firenze: **12-13%** dei pazienti è colonizzato da MRSA (pazienti con almeno una coltura/anno)

Struttura degli elementi del SCC*mec*

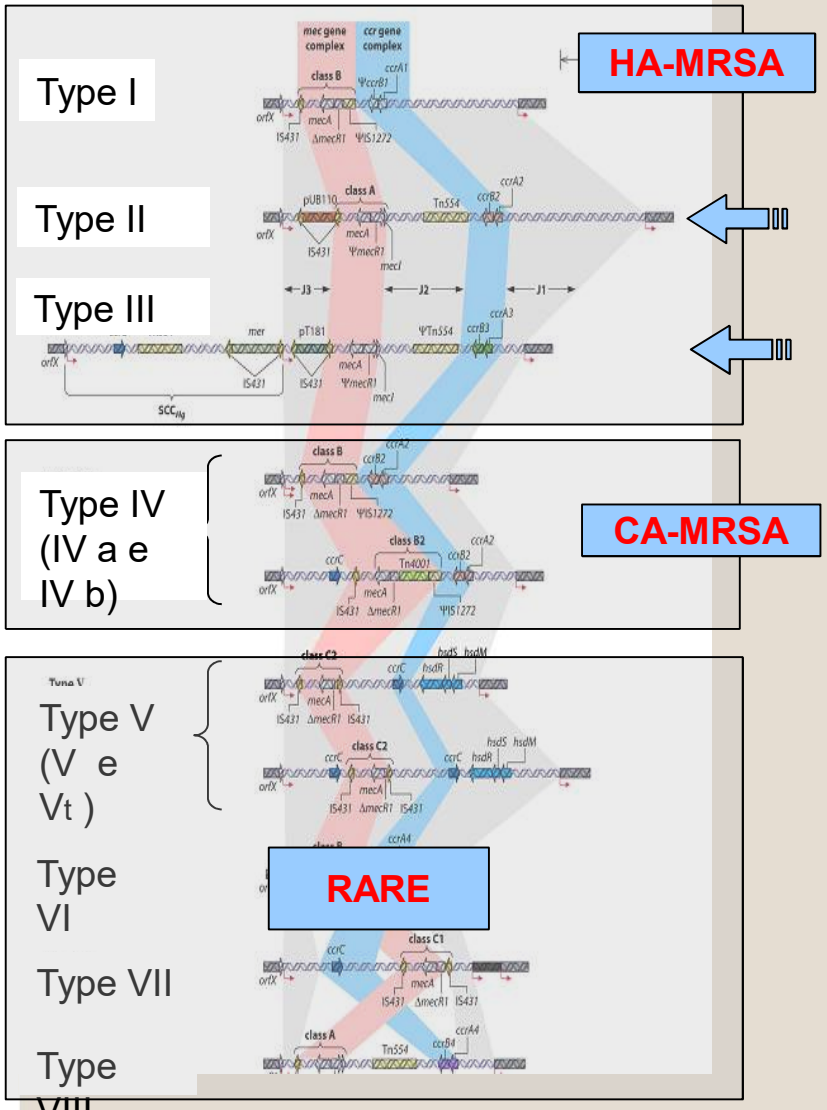
1. *mec* gene complex
Class A
Class B
Class C
Class D

2. *ccr* gene elements
Type 1 (*ccr*A1*ccr*B1)
Type 2 (*ccr*A2*ccr*B2)
Type 3 (*ccr*A3*ccr*B3)
Type 4 (*ccr*A4*ccr*B4)
Type 5 (*ccr*C)



mec* gene complex**: *gene mec (mecA) per la* ***resistenza alla meticillina e ai ß-lattamici
***ccr* gene complex**: codifica per una recombinasi che media il sito e l'orientamento di inserzione o escissione della cassetta
J-region (J1-J2-J3): parti extra ccr e mec che contengo plasimidi o transposoni che codificano per **ulteriori determinanti di resistenza** (SCC*mec* subtypes)
11 **SCC*mec* types** (8 di rilevanza clinica)

Staphylococcal cassette chromosome *mec* (SCC*mec*)



11 **SCC*mec* types** (8 di rilevanza clinica)

TABLE 1. SCC*mec* types identified in *S. aureus*

SCC*mec* type	*ccr* gene complex[a]	*mec* gene complex
I	1 (A1B1)	B
II	2 (A2B2)	A
III	3 (A3B3)	A
IV	2 (A2B2)	B
V	5 (C)	C2
VI	4 (A4B4)	B
VII	5 (C)	C1
VIII	4 (A4B4)[b]	A

[a] *ccr* genes in the gene complex are indicated in parentheses.
[b] *ccrA4B4* genes found in type VIII SCC*mec* were nearly identical to those in the *S. epidermidis* SCC-CI element and showed nucleotide identities of 89.6% and 94.5% to those found in type VI SCC*mec*.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 4961–4967

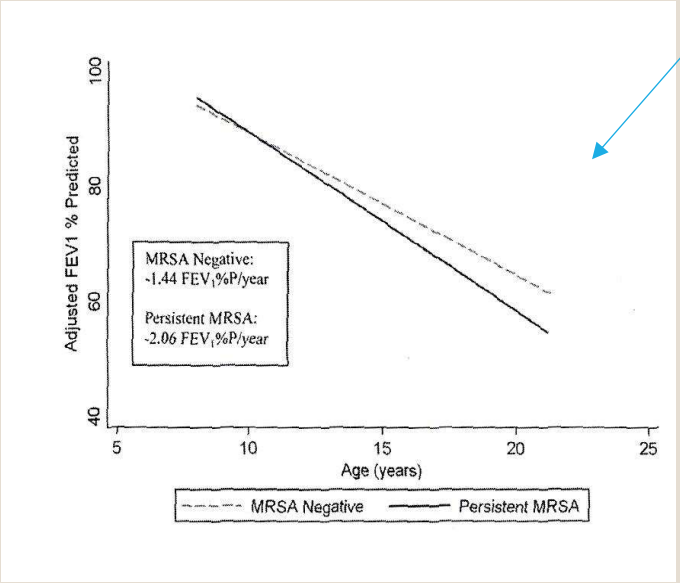
Modified from: Antimicrobiol. Agents Chemother. 2009 53: 4961-4967

HA-MRSA e CA-MRSA

	HA-MRSA	**CA-MRSA**
CARATTERISTICHE GENETICHE	SCC*mec* type I, II, III,	SCC*mec* type IV, (V)
RESISTENZE ANTIBIOTICHE	β-lattamici Macrolidi Aminoglicosidi Chinolonici Clindamicina	β-lattamici Macrolidi
Gene per la PVL	Non comune	Comune
HA-MRSA isolati prevalentemente in ospedale CA-MRSA isolati prevalentemente in comunità		

Ceppi CA-MRSA sono attualmente causa di gravi infezioni dato il loro alto grado di trasmissibilità e patogenicità: sono in grado di produrre molteplici fattori di virulenza fra cui una tossina necrotizzante, la Leucocidina di Panton Valentine (PVL)

Impatto clinico in FC:
Funzionalità polmonare e sopravvivenza



- Correlazione tra la persistenza di MRSA e il **declino della funzionalità polmonare (FEV_1)** (Dasembrook *et al*, 2008)
- Correlazione tra infezione da MRSA persistente e **sopravvivenza** dei pazienti con FC (Dasembrook *et al*, 2010)
- Fattore di **rischio per il ripristino della funzionalità polmonare** dopo esacerbazioni (Sanders et al, 2010)
- Correlazione tra MRSA persistente e **ospedalizzazione** (Harik et al, 2015)
- Correlazione con **bronchettasie**, ospedalizzazione, **declino FEV_1 doppio rispetto ai non colonizzati da MRSA** (Vanderhelst et al, 2012)

Differenze cliniche tra CA e HA

Outcomes and Treatment of Chronic Methicillin-Resistant *Staphylococcus aureus* Differs by Staphylococcal Cassette Chromosome *mec* (SCC*mec*) Type in Children With Cystic Fibrosis

Sonya L. Heltshe,[1,2] Lisa Saiman,[3,4] Elena B. Popowitch,[5,6] Melissa B. Miller,[5,6] Margaret Kloster,[2] Valeria Thompson,[2] Thomas W. Ferkol,[7,8] Wynton C. Hoover,[9] Michael S. Schechter,[10,a] and Marianne S. Muhlebach[11]

Journal of the Pediatric Infectious Diseases Society, Vol. 4, No. 3, pp. 225–31, 2015.

SCC*mec* type II (HA-MRSA):

- Antibiotici inalatori
- Più esacerbazioni

Clinical characteristics and epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in children with cystic fibrosis from a center with a high MRSA prevalence

Nada S. Harik[1], Gulnur Com, MD[1,2], Xinyu Tang, PhD, Maria Melguizo Castro, MS, Mary E. Stemper, MS, John L. Carroll, MD

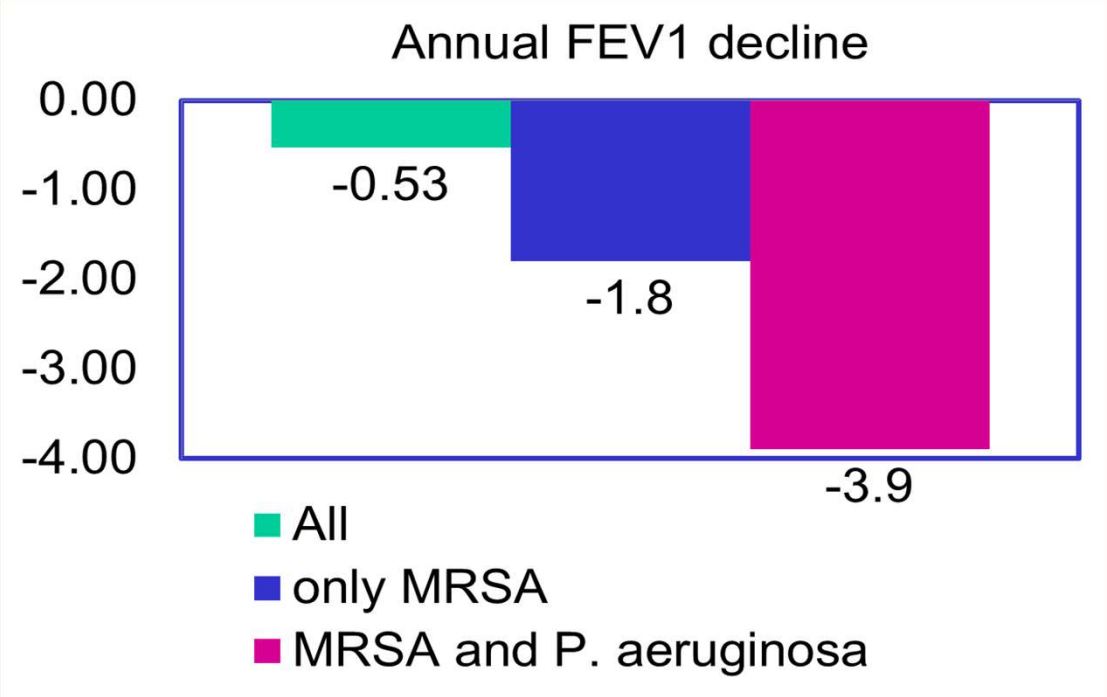
American Journal of Infection Control, April 1, 2016 Volume 44, Issue 4, Pages 409–415

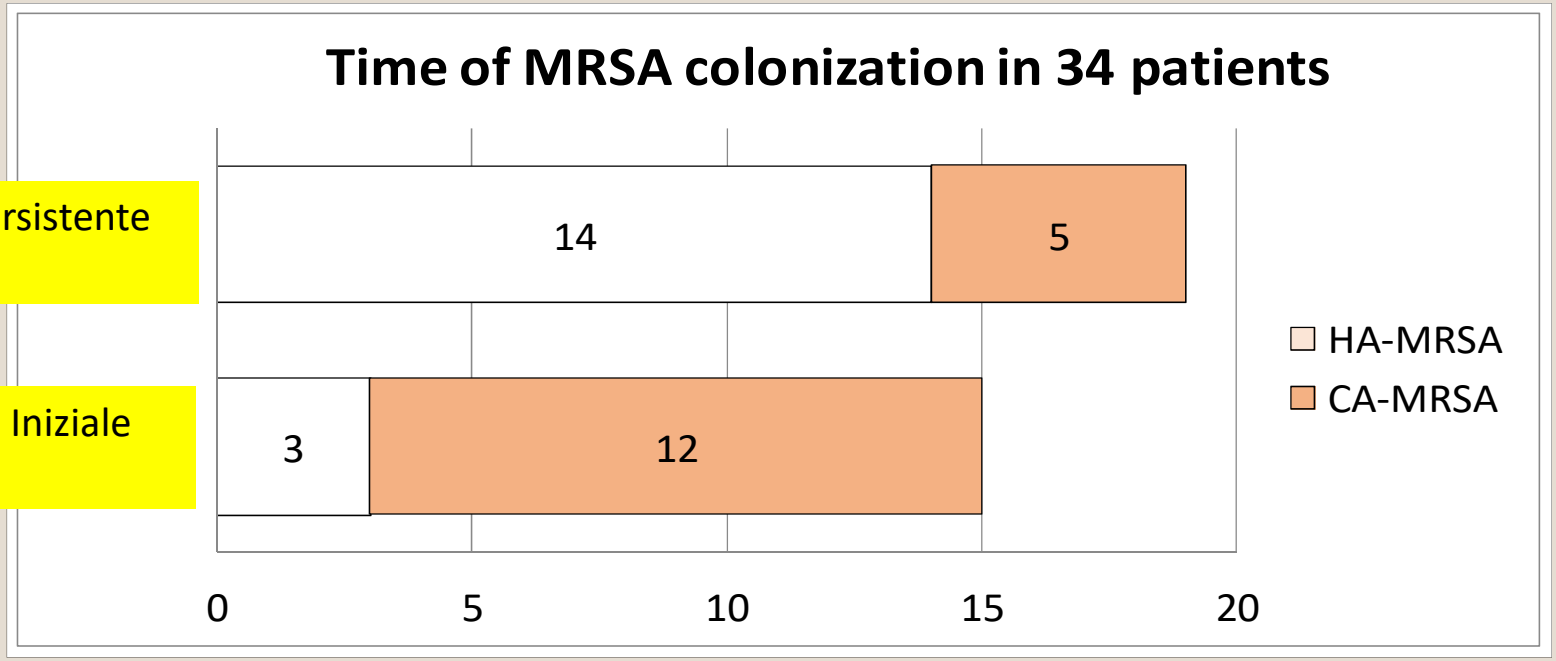
SCC*mec* type II (HA-MRSA :

- Maggiore resistenza alla clindamicina
- Maggiore numero di pazienti infettati con HA-MRSA nei pazienti FC rispetto ai non FC

Patients' description

- 66 patients with MRSA
  - 54.5% male
  - median age 17.5 yrs (range 1-52 yrs)
- 35 (53%) with first MRSA infection
- 31 (47%) intermittent or chronic MRSA infection
- Mean colonization time 1.57 ±1.24 yrs





Differentiation of MRSA colonization in CF patients: HA-MRSA versus CA-MRSA.

SCC*mec* cassette characterization

143 MRSA isolates collected from 50 (75,7%) patients were characterized by molecular method. At least one strain/ year/ patient was analyzed. DNA extraction,

50 patients	**SCC*mec* I**	**SCC*mec* II**	**SCC*mec* III**	**SCC*mec* IV**	**SCC*mec* V**	**Not ID**
Patients n° (%)	**11 (22%)**	1 (2%)	0 (0%)	**28 (56%)**	1 (2%)	9 (18%)

HA-MRSA **CA-MRSA**

MLST
Sequence type characterization

TABLE 2. Sequence variation at the seven loci

Gene	Sequence length (bp)	No. of alleles	No. of polymorphic sites
arcC	456	17	19
aroE	456	17	23
glpF	465	11	14
gmk	429	11	13
pta	474	15	18
tpi	402	14	18
yqiL	516	16	19

JOURNAL OF CLINICAL MICROBIOLOGY, 10 Mar. 2000, p. 1008–1015

A ogni profilo allelico viene assegnato un numero:
ST01
ST02
ST03
…..

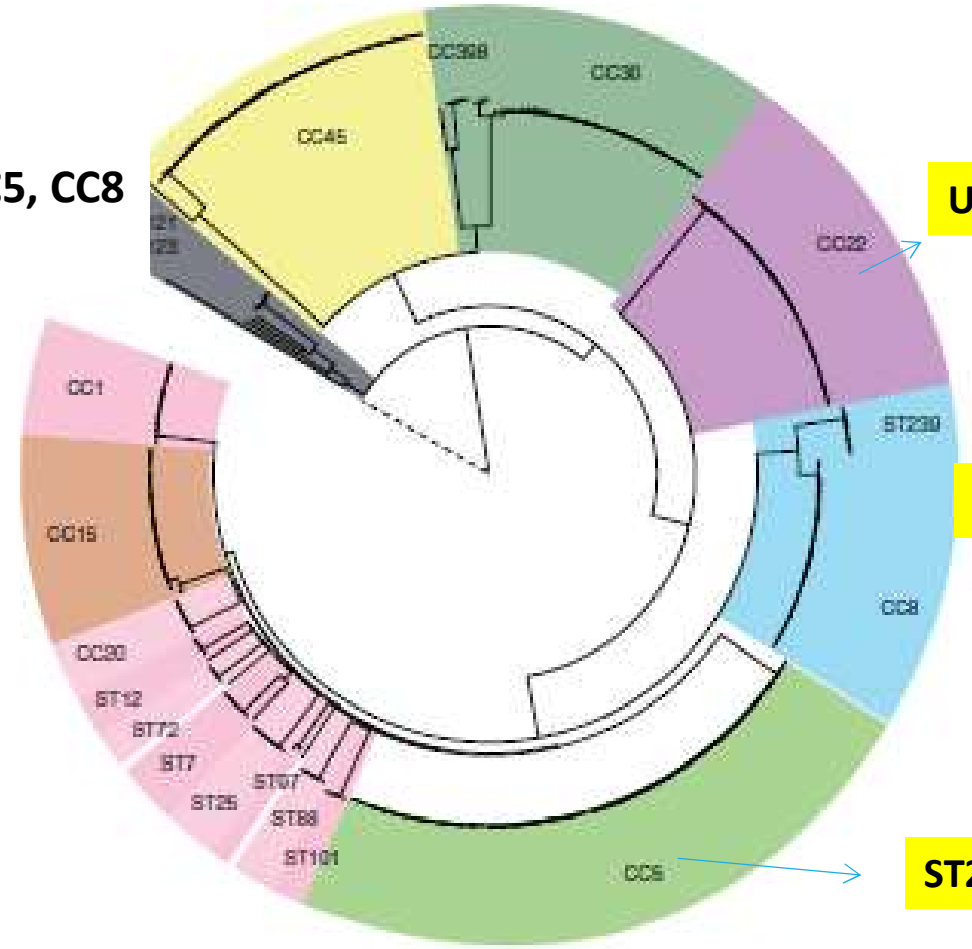
Nome del clone= profilo MLST + cassetta SCC*mec*

ST228-SCC*mec*I
ST228-I

TABLE 1 Abundance, diversity, and proportion of MRSA isolates in each major or minor CC detected in the sample

Group and CC	Total no. of genomes[a]	No. of reference genomes	Proportion of MRSA genomes[b]	Mean no. of PW SNPs (SE)[c]	Mean yr of PW MRCA (range)[d]	Example clone(s)
Major						
CC5	78	8	0.8	438 (8.2)	1951 (1950–1952)	USA100 New York/Japan USA800, pediatric
CC22	41	1	0.775	266 (6.6)	1972 (1972–1973)	EMRSA-15, Barnim
CC45[e]	39	0	0.231	571 (9.4)	1935 (1933–1936)	USA600, Berlin
CC8[f]	33	5	0.642	456 (9.1)	1949 (1948–1950)	Iberian, USA300, USA500, archaic, Central European
CC30[g]	34	2	0.065	481 (5.8)	1946 (1945–1947)	EMRSA-16 (ST36), phage type 80/81, SWP, USA200
CC15[h]	24	0	0	258 (4.4)	1974 (1973–1974)	

- **STUDIO EUROPEO**
- **380 *S. aureus* clones**
- **93% MRSA : CC22, CC5, CC8**



UK-EMRSA-15

Iberian, USA300, USA500,

ST225, ST228, ST125

FIG 1 Phylogenetic relationship of the invasive *S. aureus* population circulating in Europe in 2006. A rooted neighbor-joining tree based on 235,226 genome-wide core SNPs is shown. Lineages are highlighted and named according to the corresponding CC or ST.

Aanensen et al. May/June 2016 Volume 7 Issue 3 e00444-16 mbio.asm.org

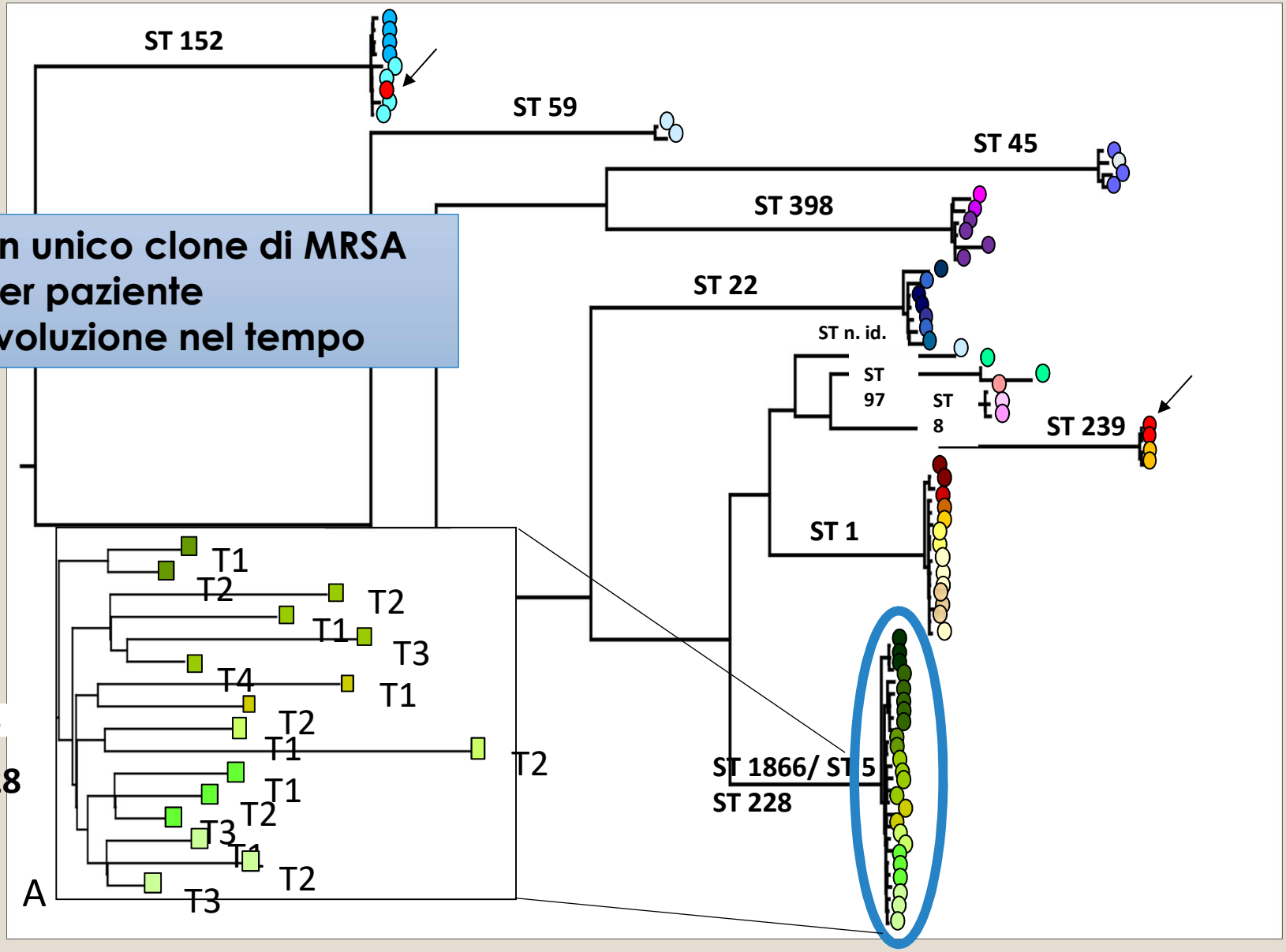
	Sequence type	SCC*mec* type	No. of patients	Related Epidemic Clones
	ST 1	III	1	-
12%	**ST 1**	IV	6	USA400 / CAMRSA-7
	ST 5	I	2	UK/EMRSA-3
	ST 5	II	1*	New York/Japan, USA100
CC8	**ST 8**	IV	3	UK-EMRSA-2/6, USA300
CC22 **22%**	**ST 22**	IV	6	UK-EMRSA-15
	ST 45	IV	2	Berlin/USA600
	ST 59	n.id.	1	(USA1000)
	ST 97	IV	1	-
14%	**ST 152**	III	3 (1°)	-
CC5 **16%**	**ST 228**	I	5	Italian/Southern German
	ST 239	III	2 (1°)	Brazilian/Hungarian
	ST 398	n. id.	2	LA-MRSA in Europe
	ST1866	II	1*	-
	ST n. id.	I	1	-

*** ST5-II and ST1866-II isolated from the same patient in different years ° ST152-III and ST239-III isolated from the same patient in different years n.id. = not identified**

Only 2 isolates (ST22 and ST152) were PVL positive.

Phylogenetic reconstruction of all isolates from 34 CF patients belonging to 15 different clones

- Un unico clone di MRSA per paziente
- Evoluzione nel tempo



Original Article

Risk factors for persistent methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis☆,☆☆

Mark T. Jennings [a,*], Elliot C. Dasenbrook [b], Noah Lechtzin [a], Michael P. Boyle [a,c], Christian A. Merlo [a]

Hazard ratios of persistent MRSA infection using Cox regression models.

Covariates	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age	0.98 (0.97–0.98)	<0.001	0.97 (0.97–0.97)	<0.001
Female sex	1.07 (1.02–1.13)	0.009	1.04 (0.98–1.10)	0.23
FEV_1% predicted, baseline	1.00 (0.99–1.00)	0.95	1.00 (0.99–1.00)	0.34
FEV_1% predicted, 10% increments [a]	0.97 (0.96–0.98)	<0.001	0.96 (0.93–0.98)	<0.001
Pancreatic Insufficiency	1.89 (1.67–2.15)	<0.001	1.49 (1.29–1.72)	<0.001
CF-related diabetes	1.15 (1.08–1.21)	<0.001	1.13 (1.05–1.20)	<0.001
F508-del homozygous	0.96 (0.91–1.01)	0.16	1.04 (0.98–1.10)	0.19
Pseudomonas aeruginosa Detected	1.32 (1.25–1.29)	<0.001	1.21 (1.13–1.28)	<0.001
B. cepacia complex detected	1.11 (0.97–1.27)	0.11	1.13 (0.97–1.31)	0.11
Higher socioeconomic status [b]	0.76 (0.72–0.80)	<0.001	0.87 (0.82–0.93)	<0.001
Chronic macrolide use	1.11 (1.04–1.17)	<0.001	1.00 (0.94–1.06)	0.99
Hospitalizations/year	1.13 (1.11–1.14)	<0.001	1.09 (1.06–1.12)	<0.001
Number of days receiving IV antibiotics in the hospital/year	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.37
Number of days receiving IV antibiotics at home/year	1.00 (1.00–1.00)	0.05	1.00 (1.00–1.00)	0.02
CF center MRSA prevalence				
Quartile 1	1.00	NA	1.00	NA
Quartile 2	0.80 (0.76–0.85)	<0.001	1.39 (1.27–1.52)	<0.001
Quartile 3	1.25 (1.18–1.32)	<0.001	1.81 (1.66–1.97)	<0.001
Quartile 4	1.65 (1.55–1.75)	<0.001	2.33 (2.13–2.56)	<0.001

[a] Change in FEV_1% predicted during follow up.

[b] Higher socio-economic status determined by use of private insurance.

M.T. Jennings et al. / Journal of Cystic Fibrosis xx (2017) xxx–xxx
Received 9 December 2016; revised 3 April 2017; accepted 4 April 2017

Riassumendo

- **L' epidemiologia di MRSA è molto varia**, con grandi differenze geografiche.
- L'infezione da MRSA ha un **impatto sull'outcome clinico**: decremento FEV_1, maggiorni esacerbazioni, ospedalizzazioni e uso di antibiotic (**NUOVA SFIDA IN FC**)
- Molti pazienti FC sono infettati persistentemente da **un unico clone di MRSA con differenze tra** colonizzazioni da **CA-MRSA e gli HA-MRSA**
- I cloni di MRSA trovati in FC appartengono a **cloni conosciuti** e già descritti in letteratura, che circolano in comunità e in ospedale
- I dati suggeriscono l'importanza dello studio del background genetico di MRSA per studiarne l'epidemiologia e **migliorare il management clinico** di queste infezioni (➔ **Infection control, protocolli di eradicazione del germe**)

GRAZIE PER L'ATTENZIONE

Patients' description

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Pattern di resistenza antibiotica isolati MRSA non FC