Allosteric site missense mutations in PBP2A affecting ceftaroline susceptibility detected in epidemic HA-MRSA clonotypes ST228 and ST247 in Western Switzerland

eP180

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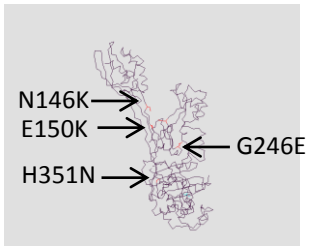
Background

- Methicillin-resistance in *S. aureus* depends on acquisition of *mecA*, encoding PBP2A, a cell wall protein refractory to inhibition by several β-lactams.
- **CEFTAROLINE, a novel β-lactam cephalosporin binds PBP2A. Ceftaroline has good activity against MRSA.**
- Some resistant isolates observed around the world (EUCAST MIC >1 mg/l or CLSI MIC ≥4 mg/L)

Allosteric site (AS)

Transpeptidase Domain (TD)



Mutations decreasing Ceftaroline affinity (Mendes *et al* 2012)

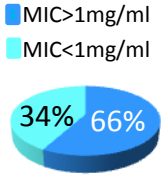
Ceftaroline binds to AS and TD (Otero *et al* 2013)

In this study, we analysed efficacy of ceftaroline using a collection of archived MRSA (1994-2003) in our hospital

Results

1. Ceftaroline susceptibility

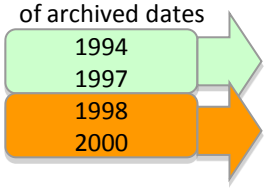
1.Tested by disc diffusion and microdilution MIC assays.
2. EUCAST recommendations:
If diameter between 19-21mm, a MIC determination will confirm susceptibility.



Unprecedented observation: 66% of our MRSA strain set is considered resistant.

2. Detailed examination of susceptibility data

Chronological order of archived dates



Strains before 1998 are susceptible

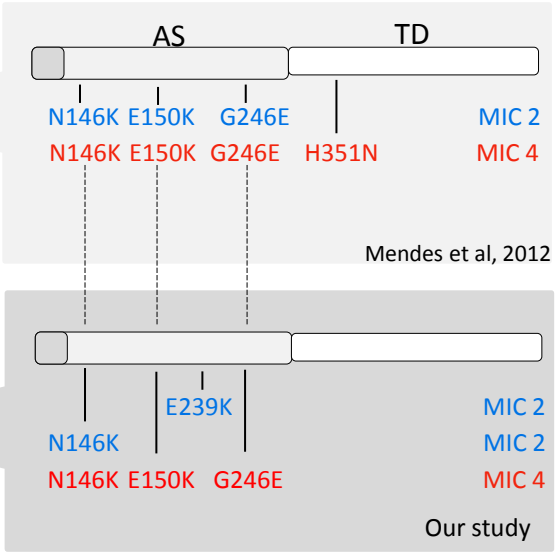
Strains after 1998 are predominantly resistant

Around 1998, arrival of aggresive nosocomial MRSA ST228 to our hospital

3. SCCMec, ST type and PBP2A sequencing

Hypothesis: MRSA collection containing predominantly ST228 type strains contains PBP2A features linked to ceftaroline resistance

Strain Collection	Archived Date	ST / SSCmec type	MIC	PBP2A Mut
Greece		ST5 SCCMec II	1	
Greece		ST239 SCCMec III	2	2*
Greece	2008	ST239 SCCMec III	4	3*
HUG	1994	ST30 SCCMec III	0.5	
HUG	1995	ST30 SCCMec III	0.5	
HUG	1996	ST45 SCCMec IV	0.5	
HUG	1996	ST572 SCCMec I	1	
HUG	1997	ST45 SCCMec IV	0.5	
HUG	1997	ST45 SCCMec IV	1	
HUG	1998	ST30 SCCMec III	1	
HUG	1998	ST247 SCCMec I	4	3*
HUG	1998	ST247 SCCMec I	4	3*
HUG	1998	ST228 SCCMec I	2	E239K
HUG	1998	ST228 SCCMec I	2	E239K
HUG	1999	ST45 SCCMec IV	0.5	
HUG	1999	ST228 SCCMec I	2	N146K
HUG	1999	ST228 SCCMec I	2	N146K
HUG	1999	ST228 SCCMec I	2	N146K
HUG	2000	ST228 SCCMec I	2	N146K
HUG	2000	ST228 SCCMec I	2	N146K
HUG	2000	ST228 SCCMec I	2	N146K
HUG	2000	ST228 SCCMec I	4	N146K
HUG	2001	ST228 SCCMec I	1	N146K
HUG	2001	ST228 SCCMec I	1	N146K
Lausanne	2001	ST228 SCCMec I	2	N146K
Lausanne	2001	ST228 SCCMec I	2	N146K
HUG	2002	ST228 SCCMec I	2	N146K
HUG	2003	ST8 SCCMec IV	0.5	N146K
HUG	2003	ST228 SCCMec I	2	N146K
HUG	2003	ST228 SCCMec I	2	N146K
Lausanne	2006	ST228 SCCMec I	2	N146K
Lausanne	2006	ST228 SCCMec I	2-4	N146K
Lausanne	2006	ST228 SCCMec I	2	N146K
Lausanne	2008	ST228 SCCMec I	2	N146K
Lausanne	2008	ST228 SCCMec I	2	N146K
Lausanne	2008	ST228 SCCMec I	2	N146K
HUG		ST250	0.25	
HUG		ST5 SCCMec II	1	



1. Strains showing MIC > 1mg/L were predominantly ST228 but also ST247 containing mutations in PBP2A allosteric site.

2. Lausanne MRSA ST228 strains also show MIC>1mg/L and mutations in PBP2A allosteric site.

3. We observed the same single mutation in both ST228 strains with MIC 4 and MIC 2, supporting the notion that other factors are important.

Conclusions

- **PBP2A allotypes in certain localized epidemic strains can influence susceptibility to newly introduced PBP2A directed antibiotics.**
- **Reduced susceptibility detected long before introduction of ceftaroline. Do other antibiotics select for PBP2A mutations with potentially far-reaching consequences ?**

•This work was conducted in part by support from an investigator-initiated ISSP grant of AstraZeneca and Swiss national science foundation grants WLK 10030 -1465450 and AR 310030 -149762. We acknowledge « Laboratoire de typage microbien » Dr. D. Blanc and J. Bille from CHUV hospital (Lausanne, Switzerland) for kindly providing their sequenced MRSA ST228 strains (Vogel 2012: PlosOne 7(6):e38969).