S.aureus endocarditis in the course of SAB: the bug or the host ?

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Staphylococcus aureus Infective Endocarditis

- IE : 10 to 40 % of *S.aureus* bacteremia
- Predisposing factors: at risk cardiopathy, IV drug user, previous IE..
  - Not all of those patients develop IE
  - Patients with no risk factors develop IE
- What else play a role ?

Rasmussen RV 2011; Selton-Suty C 2012, Joseph JP 2013; Chang FY; Fowler VG 1997; Hill EE 2007; Forsblom E 2011; Bayer A 1987; Van Hall 2005; Sullenberger 2005; Jenkins TC 2008; Le Moing V 2015

Factors affecting the occurrence of IE in the course of bacteremia

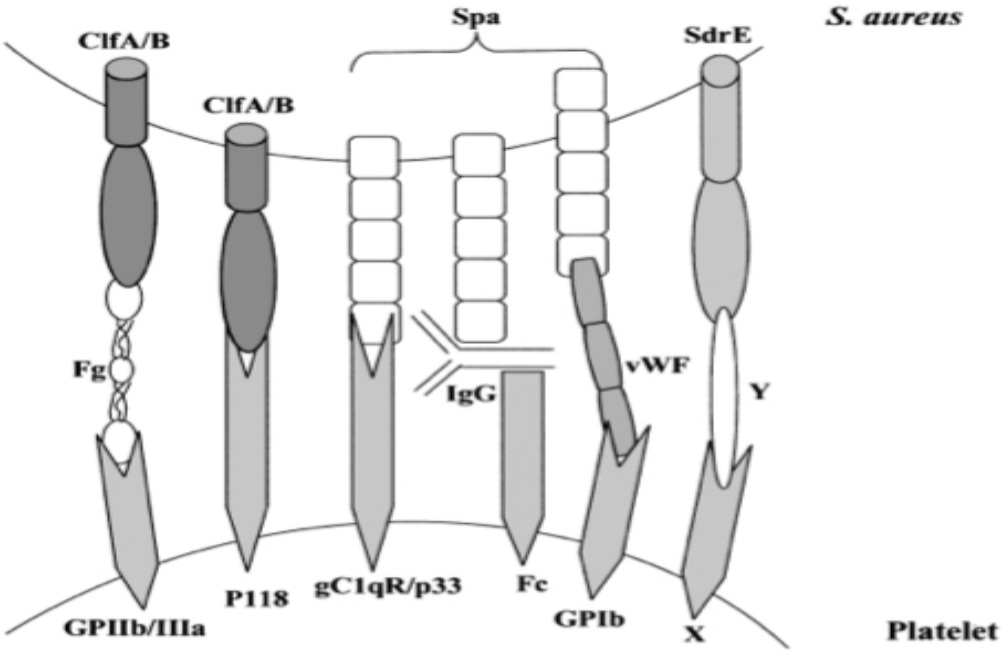
- Predisposing factors: at risk cardiopathy, IV drug user, previous IE..
- The bug: pathovars associated with IE ?
- The host: genetic predisposition associated with IE ?

Factors affecting the occurrence of IE in the course of bacteremia

- Predisposing factors: at risk cardiopathy, IV drug user, previous IE..
- The bug: pathovars associated with IE ?
- The host: genetic predisposition associated with IE ?

Pathogenesis of IE: candidates from in vitro/ animal

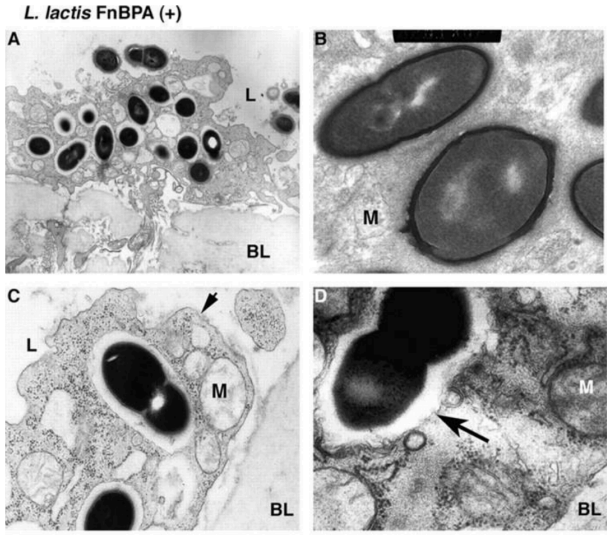
- clumping factor A–B
- fibronectin-binding protein A–B
- collagen-binding protein
- SdrD/E
- Protein A
- Coagulase, vWFbp



Entenza et al. Infect Immun (2005)
O'Brien et al. Mol Microbiol (2002)
Hienz et al. J Infect Dis (1996)
Panizzi P et al. Nat Med (2011)
Vanassche T et al. Thromb Haemost (2012), Claes et al. Blood (2014)J

Pathogenesis: factor known to play a role in pathogenesis in vitro/animal

- polysaccharide intercellular adhesin -> biofilm
- Cell internalisation
- Staphylococcal superantigens
  - SEC, TSST-1, EGC



Que YA et al. J exp Med (2005)

Zhu Y et al. Infect Immun (2009)
Que YA et al. J exp Med (2005)
Salgado-Pabón et al. Mbio (2013)
Stach et al. PLOS ONE (2016)

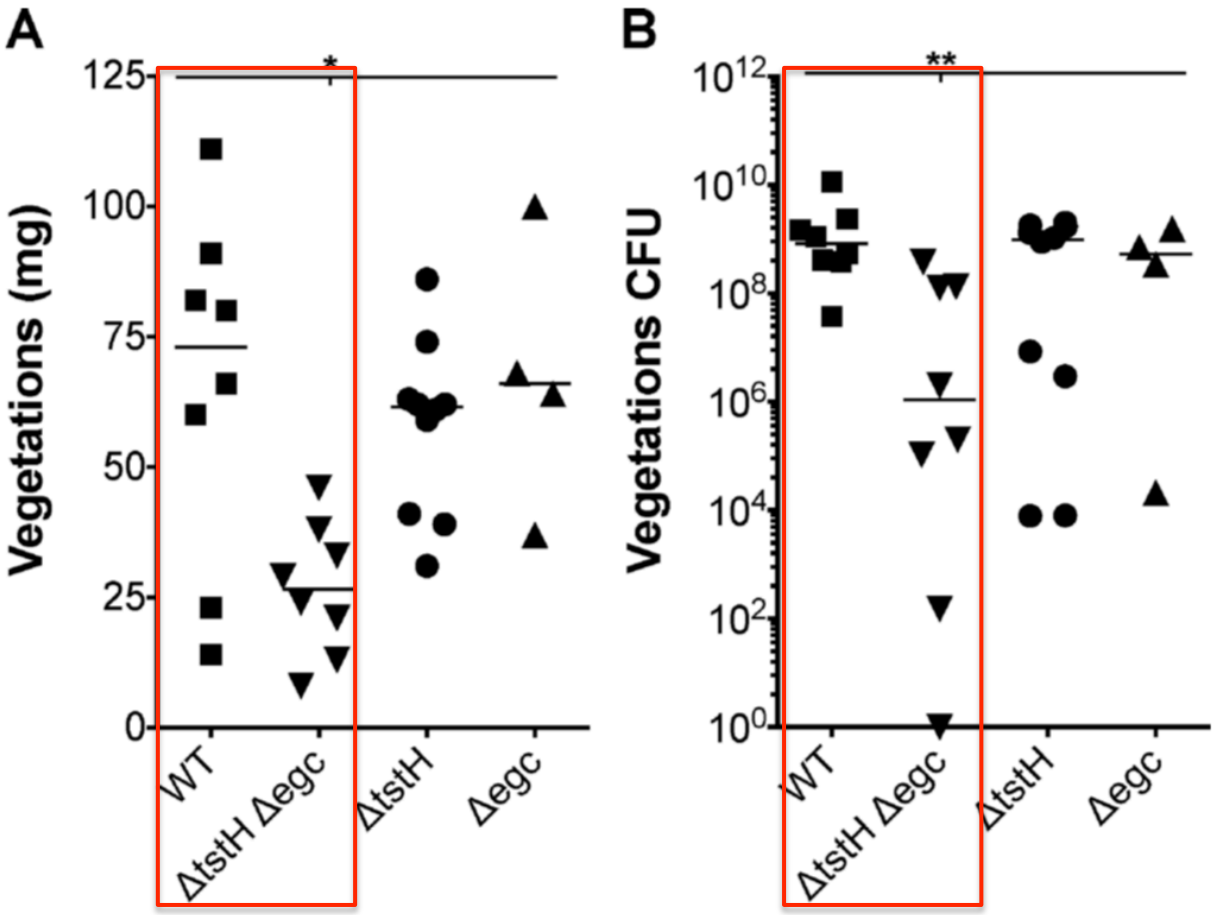


Fig 3. The *egc* SAgs and TSST-1 are involved in vegetation formation during IE. (*A*) Total weight of vegetations dissected from aortic valves after intravenous inoculation of 3–4 x 10^8 CFU of wild-type MN8, MN8Δ*tstH*Δ*egc*, MN8Δ*tstH*, or MN8Δ*egc*. (*B*) Bacterial counts recovered from vegetations shown in panel A. **P* = 0.01, ***P* = 0.03, one-way ANOVA and non-parametric, Kruskal-Wallis test. Horizontal lines represent the median. $P \leq 0.05$ is considered statistically significant.

The egc SAgs and TSST-1 are involved in vegetation formation during IE in rabbit

Salgado-Pabón et al. Mbio (2013)

Staphylococcus aureus endocarditis: distinct mechanisms of bacterial adhesion to damaged and inflamed heart valves

Laurens Liesenborghs[1], Severien Meyers[1], Marleen Lox[1], Maarten Criel[1], Jorien Claes[1], Marijke Peetermans[1], Sander Trenson[1], Greetje Vande Velde[2], Pieter Vanden Berghe[3], Pieter Baatsen[4], Dominique Missiakas[5], Olaf Schneewind[5], Willy E. Peetermans[6], Marc F. Hoylaerts[1], Thomas Vanassche[1], and Peter Verhamme[1]*

New IE model in mice
-mechanical damage-induced: **VWF-binding protein** and **Clumping factor A**.
-inflammation-induced: **platelet** in a **sortase-independent** manner

Liesenborghs, European Heart Journal (2019)

Pathogenesis of IE: summary of in vitro/animal

- Interactions with matrix proteins and platelets
- Manipulation of the host coagulation cascade
- Biofilm
- Cell internalisation
- Immune evasion via superantigens

→ Strains equipped with these virulence factors should be more prone to cause IE during SAB

Clinical correlates ?

Strains from IE versus SAB only cases

IE vs bacteremia: Specific lineages ?

Table 1. A comparison of the population structures of methicillin-susceptible *Staphylococcus aureus* isolates from patients with infective endocarditis (IE) or bloodstream infection (BSI) without IE[a].

MLST Clonal complex (CC)[b]	IE isolates (%), n = 89	non-IE BSI isolates (%), n = 81	P-value[c]
CC45	16 (18.0)	14 (17.3)	1.000
CC5	16 (18.0)	15 (18.5)	1.000
CC15	11 (12.4)	4 (4.9)	0.108
CC30	11 (12.4)	11 (13.6)	0.823
CC8	8 (9.0)	10 (12.3)	0.619
CC398	5 (5.6)	2 (2.5)	0.447
Others	22 (24.7)	25 (30.9)	0.395

[a]IE and non-IE isolates were collected in 2008 and 2006, respectively.
[b]MLST Clonal Complexes were inferred from microarray analysis.
[c]P-values were calculated for each CC using a two-tailed Fisher's exact test. The P-value for the whole contingency table was 0.592.
doi:10.1371/journal.pone.0051172.t001

- 89 IE isolates: French national population- based survey, 2008
- 81 bacteremia isolates: French isolates 23 University Hospitals, 2006-2007
- -> No significant association between IE isolates and specific CC

Selton-Suty CID (2012)
Grundmann,PLOS Med (2010)
Tristan, PLoS ONE (2012)

? Specific lineages : VIRSTA cohort

Clonal Complex (CC)	IE isolates (%) n = 72	Bacteremia isolates (%) n = 54	*P*-value [(a)]
CC5	13 (18.1)	12 (22.2)	0.65
CC45	10 (13.9)	5 (9.3)	0.58
CC30	5 (6.9)	7 (13)	0.36
CC15	11 (15.3)	2 (3.8)	*0.04*
CC8	7 (9.7)	4 (7.4)	0.76
CC398	6 (8.3)	2 (3.8)	0.46
Others [(a)]	18 (25)	22 (40.7)	0.08

- 72 definite IE
- 54 Bacteremia controls: excluded IE(1) + negative TEE mandatory
- -> No significant association between IE isolates and specific CC

Le Moing, PLOS One 2015; Bouchiat, Inf Genet Evol 2015

Virulence factors:IE vs bacteremia

Table 2. A comparison of the genotypic profiles of methicillin-susceptible *Staphylococcus aureus* isolates from patients with infective endocarditis (IE) or bloodstream infection (BSI) without IE[a].

Gene or allele	IE isolates (%), n = 89	non-IE BSI isolates (%), n = 81	P-value[b]
Adhesins			
fnbA	89 (100.0)	79 (97.5)	0.226
fnbB	76 (85.4)	70 (86.4)	1.000
clfA	89 (100.0)	81 (100.0)	1.000
clfB	89 (100.0)	81 (100.0)	1.000
cna	37 (41.6)	33 (40.7)	1.000
spa	89 (100.0)	81 (100.0)	1.000
sdrC	89 (100.0)	81 (100.0)	1.000
sdrD	73 (82.0)	62 (76.5)	0.449
bbp	78 (87.6)	78 (96.3)	0.051
ebpS	89 (100.0)	81 (100.0)	1.000
map/eap	85 (95.5)	80 (98.8)	0.370
Toxins			
eta	0 (0.0)	1 (1.2)	0.476
etb	0 (0.0)	0 (0.0)	1.000
tst	8 (9.0)	16 (19.8)	0.050
sea	16 (18.0)	17 (21.0)	0.699
seb	1 (1.1)	5 (6.2)	0.104
sec	16 (18.0)	12 (14.8)	0.680
sed	5 (5.6)	4 (4.9)	1.000
see	0 (0.0)	0 (0.0)	1.000
seg	52 (58.4)	55 (67.9)	0.209
seh	6 (6.7)	6 (7.4)	1.000
sei	51 (57.3)	56 (69.1)	0.116
sej	5 (5.6)	4 (4.9)	1.000
pvl	0 (0.0)	0 (0.0)	1.000

- IE isolates from a population-based survey
- Bacteremia isolates from 23 university hospital
- ➔ No virulence encoding gene associated with IE

Selton-Suty CID (2012)
Grundmann,PLOS Med (2010)
Tristan, PLoS ONE (2012)

Table II. Frequency of genes detected by DNA microarray in *S. aureus* IE and bacteremia strains.

Gene or allele	IE isolates (%) n = 72	Bacteremia isolates (%) n = 54	*P*-value[a]
Adhesins encoding genes			
fnbA	72 (100)	54 (100)	1.00
fnbB	65 (90.3)	46 (85.2)	0.42
clfA	72 (100)	54 (100)	1.00
clfB	72 (100)	54 (100)	1.00
cna [b]	32 (44.4)	26 (48.1)	0.72
spa	72 (100)	54 (100)	1.00
sdrC	72 (100)	53 (98.1)	0.43
sdrD	56 (77.8)	43 (79.6)	0.83
bbp	66 (91.7)	49 (90.7)	1.00
ebpS	72 (100)	54 (100)	1.00
map/eap	71 (98.6)	48 (88.9)	0.04
Toxins encoding genes			
etA	1 (1.4)	1 (1.9)	1.00
etB	0 (0)	1 (1.9)	0.43
tst1	7 (9.7)	8 (14.8)	0.42
seA	12 (16.7)	5 (9.3)	0.30
seB	6 (8.3)	8 (14.8)	0.27
seC	10 (13.9)	2 (3.7)	0.07
seD	7 (9.7)	5 (9.3)	1.00
seE	0 (0)	0 (0)	1.00
seG	34 (47.2)	35 (64.8)	0.07
seH	2 (3.2)	4 (7.4)	0.40
seI	34 (47.2)	35 (64.8)	0.07
seJ	7 (9.7)	5 (9.3)	1.00
*luk*SF-PV	0 (0)	4 (7.4)	0.03
hla [c]	71 (98.6)	49 (90.7)	1.00
hlb^{125} [d]	48 (66.7)	44 (81.5)	0.07
func_hlb [e,f]	9 (12.5)	9 (16.7)	0.60
Other putative virulence factors encoding genes			
icaA	72 (100)	54 (100)	1.00
chp [g]	46 (63.9)	32 (59.3)	0.45
Regulation encoding genes			
agrI	33 (45.8)	22 (40.7)	0.59
agrII	28 (38.9)	17 (31.5)	0.45
agrIII	8 (11.1)	11 (20.4)	0.21
agrIV	3 (4.2)	4 (7.4)	0.46

Virulence factors: IE vs bacteremia

VIRSTA

- 72 definite IE
- 54 Bacteremia IE-excluded
- ➔ No virulence encoding gene associated with IE

Le Moing, PLOS One 2015
Bouchiat, Inf Genet Evol 2015

WGS ?

MICROBIAL GENOMICS

RESEARCH ARTICLE

Lilje *et al.*, *Microbial Genomics* 2017;3

DOI 10.1099/mgen.0.000138

MICROBIOLOGY SOCIETY

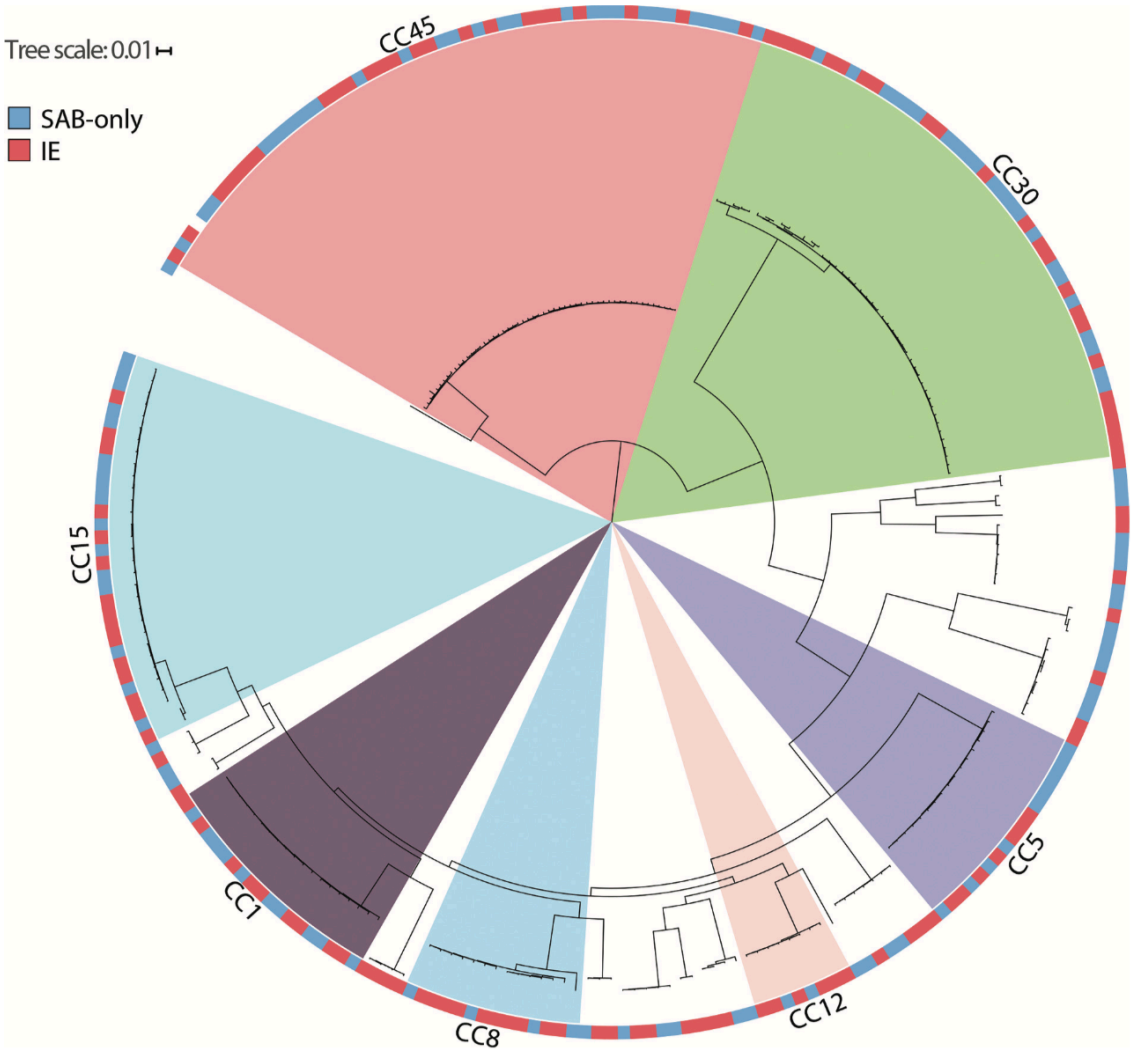
OPEN DATA OPEN MICROBIOLOGY

Whole-genome sequencing of bloodstream *Staphylococcus aureus* isolates does not distinguish bacteraemia from endocarditis

Berit Lilje,[1] Rasmus Vedby Rasmussen,[2] Anders Dahl,[2] Marc Stegger,[1] Robert Leo Skov,[1] Vance G. Fowler Jr,[3] Kim Lee Ng,[1] Kristoffer Kiil,[1] Anders Rhod Larsen,[1] Andreas Petersen,[1] Helle Krogh Johansen,[4] Henrik Carl Schønheyder,[5] Magnus Arpi,[6] Flemming S. Rosenvinge,[7] Eva Korup,[8] Ulla Høst,[2] Christian Hassager,[9] Sabine Ute Alice Gill,[10] Thomas Fritz Hansen,[2] Thor Bech Johannesen,[2] Jesper Smit,[11] Peter Søgaard,[12] Paal Skytt Andersen[1,13,14,*] and Niels Eske-Bruun[15]

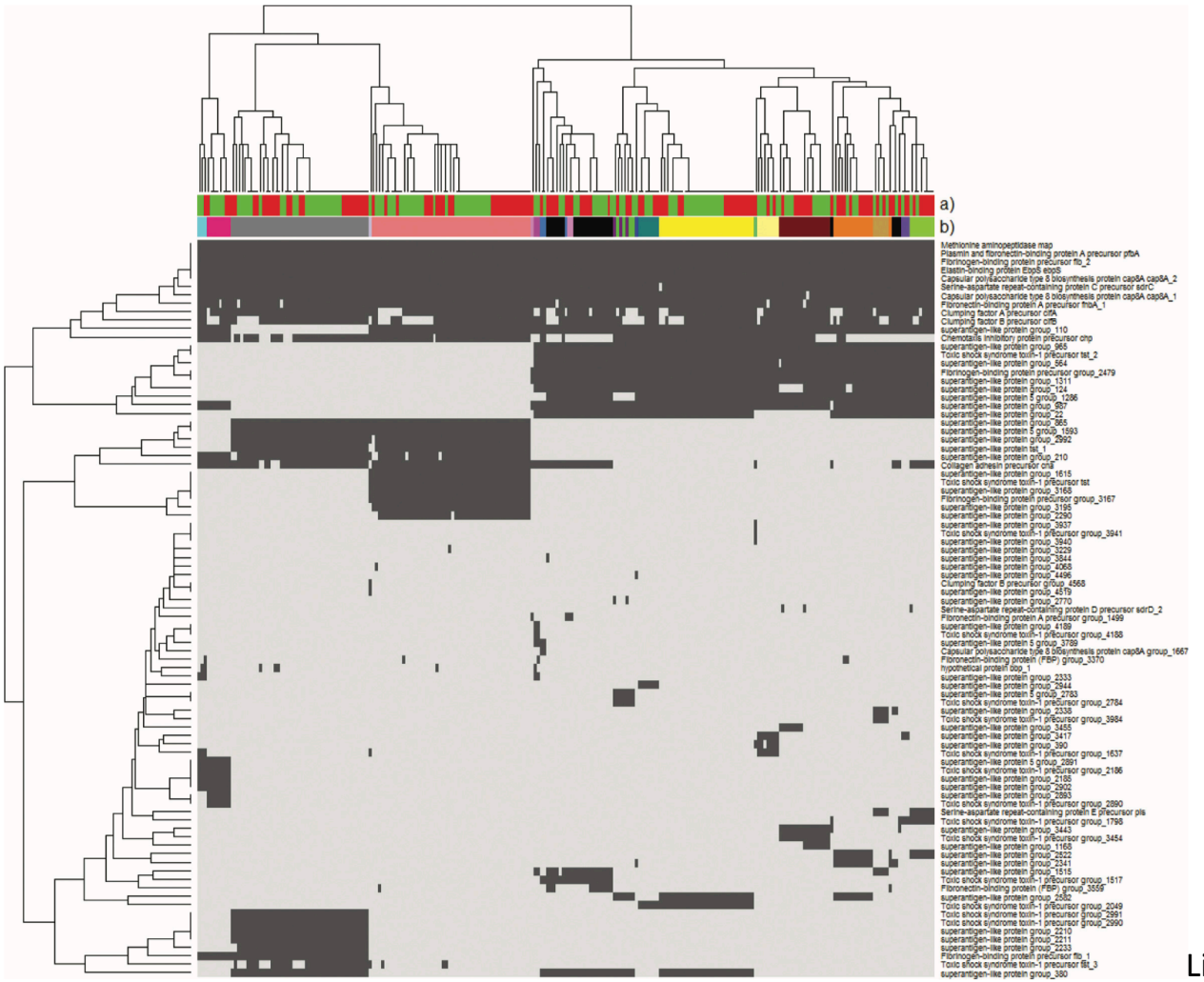
Method

- 120 Definite IE, 121 IE-Excluded Bacteremia
- WGS
- CC analysis
- SNP univariate and multivariate (DAPC)
- Accumulation of SNPs
- Accessory genome (Prokka)
- K-mer (30bps) analysis



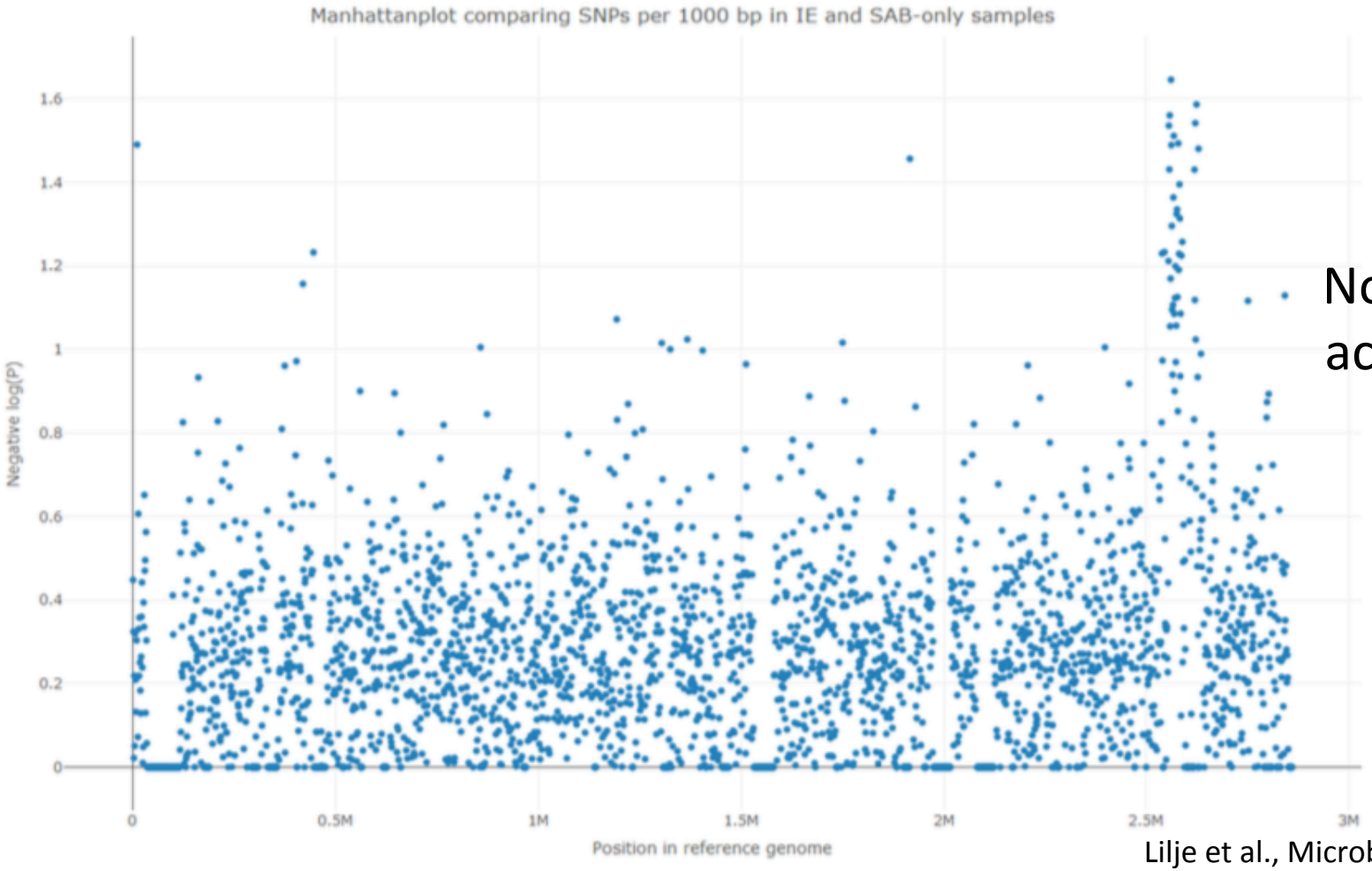
No single CC significantly associated to SAB-only or to IE

Lilje et al., Microbial Genomics 2017



None of the virulence genes associated with IE or SAB-only

Lilje et al., Microbial Genomics 2017



No significant accumulation of SNPS in 1000 bp window

Lilje et al., Microbial Genomics 2017

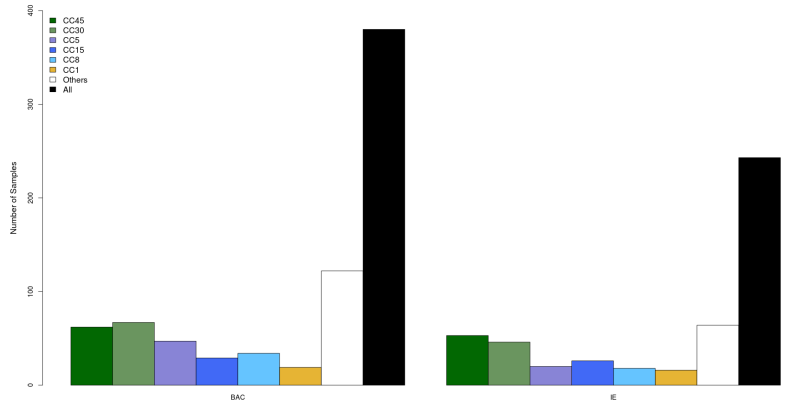
GWAS on larger sample size

- 623 samples
  - 380 IE-excluded Bacteremia
  - 243 Duke definite Infective Endocarditis
- Analysis
  - Virulome, regulome, nc-RNA
  - Genes
  - SNPs
  - Kmer
  - dbGWAS

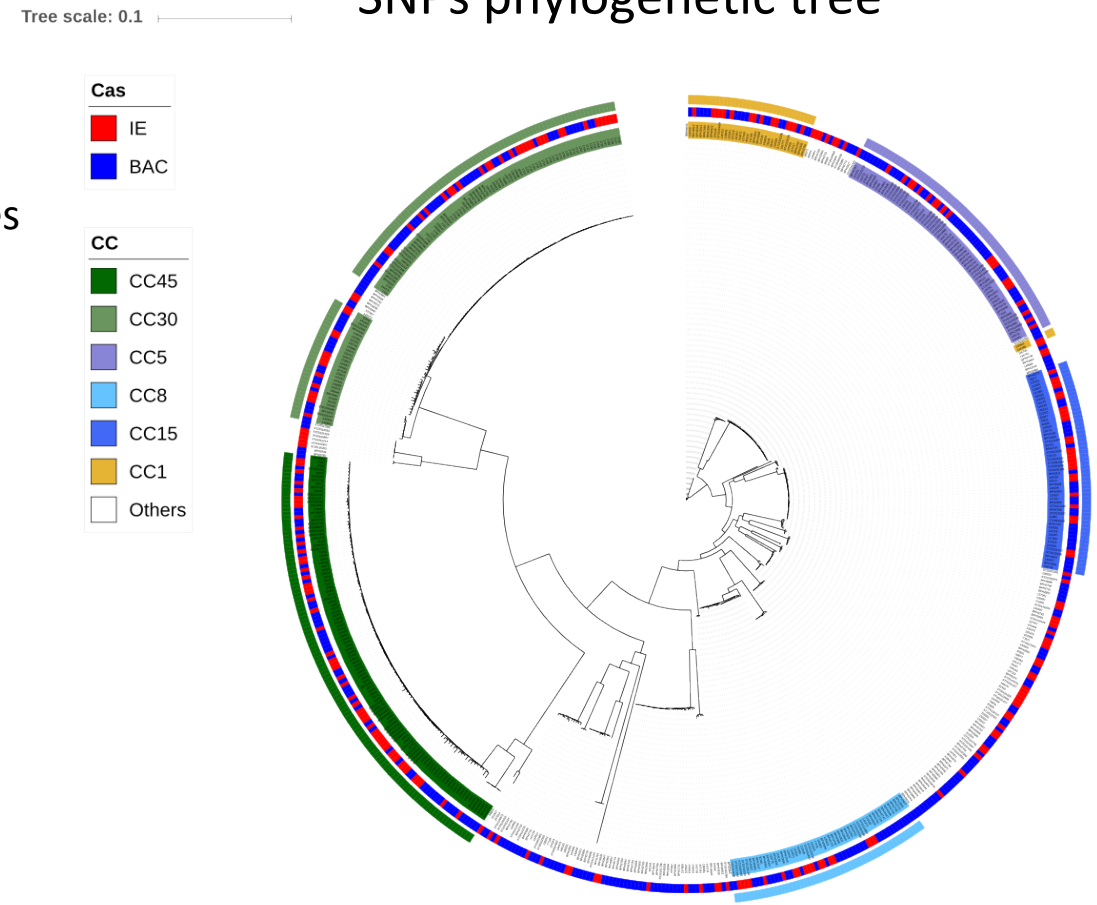
Sequence Typing

- 33 CCs
- 6 CCs -> 70% of total samples

(CC : 45, 30, 5, 8, 15, 1)



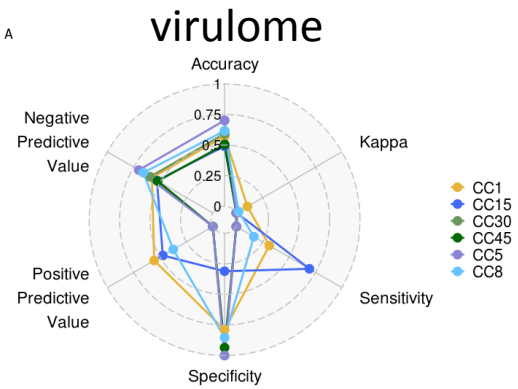
SNPs phylogenetic tree

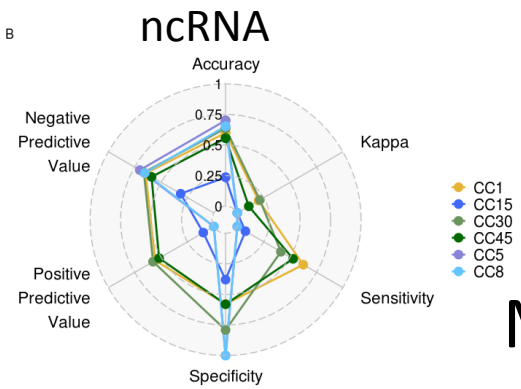


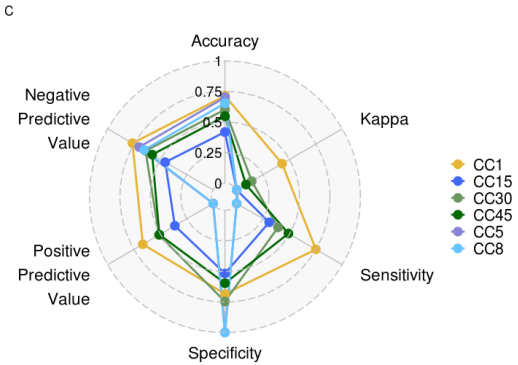
Rooted Phylogenetic tree based on the 156991 SNPs from the 623 *S. aureus* strains.
Reference genome : MSSA476 (CC1)

GWAS Virulome

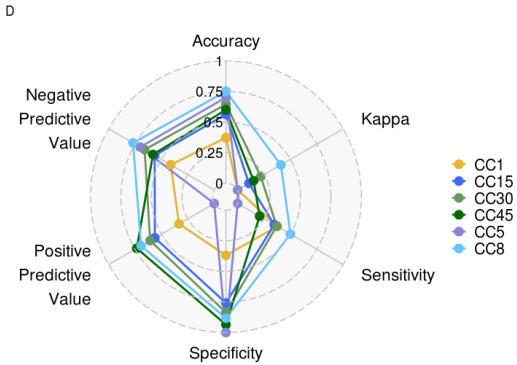
Sylvere Bastien, unpublished







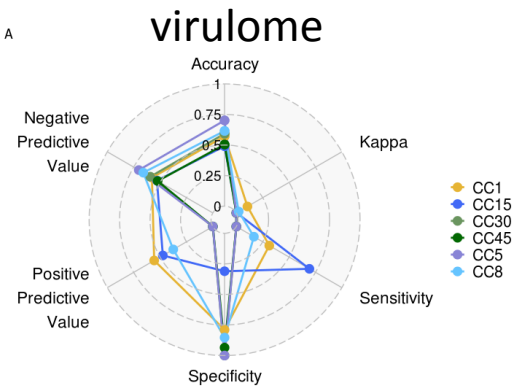
Genes

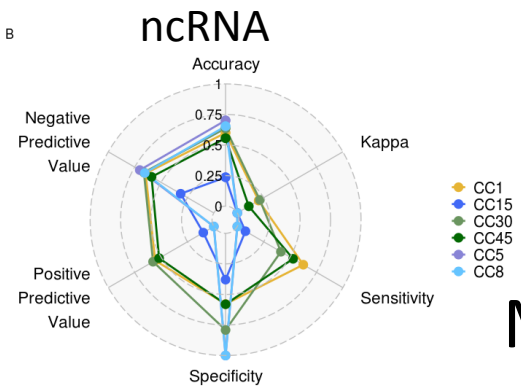


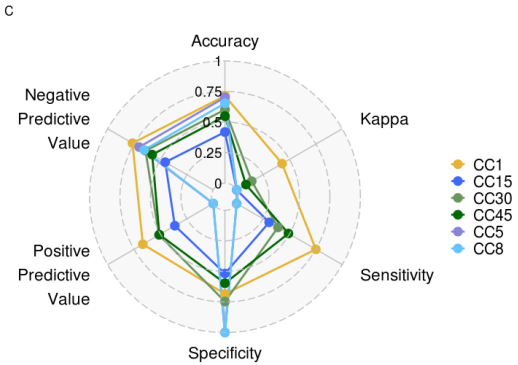
SNPs

Machine learning approach: Random Forest

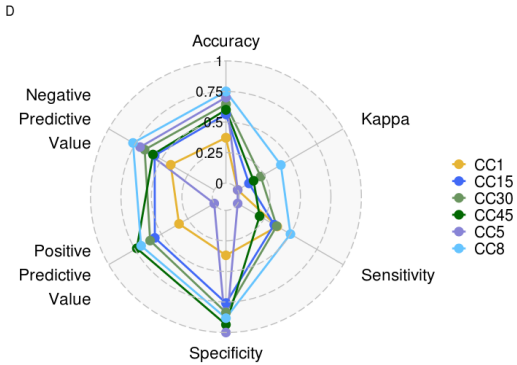
Sylvere Bastien, unpublished







Genes

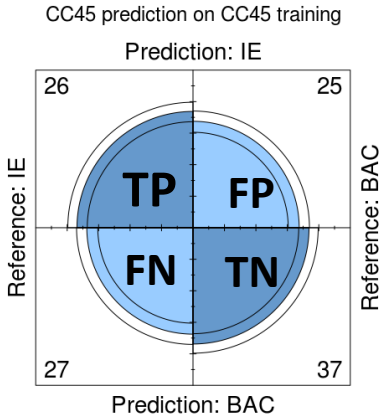


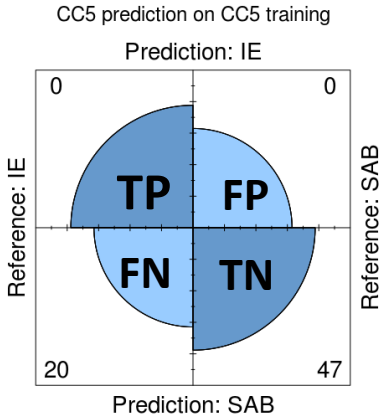
SNPs

Machine learning approach: Random Forest

Overall poor performance

Sylvere Bastien, unpublished

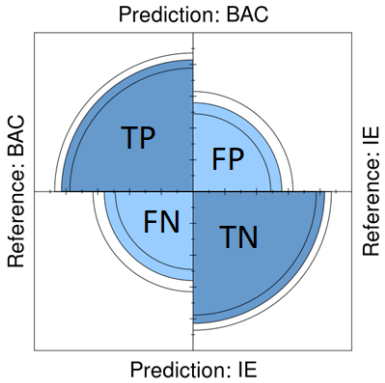




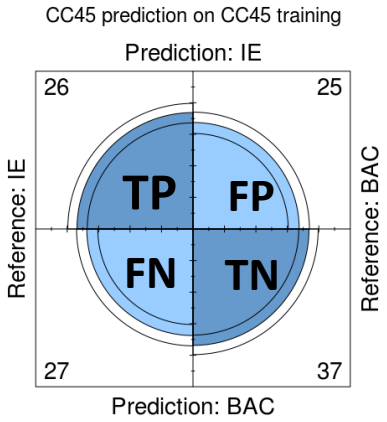
Random Forest predictions

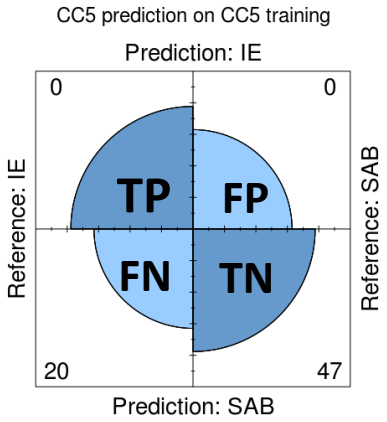
CC5 and CC45 (highest number of samples)

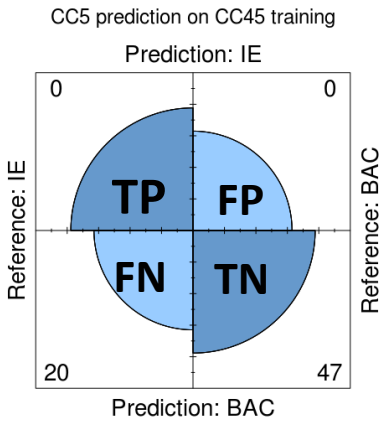
Exemple of A good prediction

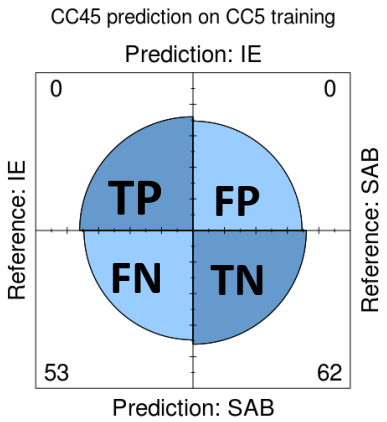


Sylvere Bastien, unpublished









Random Forest predictions

CC5 and CC45 (highest number of samples)

-> Predictions are not accurate

-> Predictors seem not to be shared between CCs

Sylvere Bastien, unpublished

WGS ?

MICROBIAL GENOMICS

RESEARCH ARTICLE

Lilje *et al.*, *Microbial Genomics* 2017;3

DOI 10.1099/mgen.0.000138

MICROBIOLOGY SOCIETY

OPEN DATA OPEN MICROBIOLOGY

Whole-genome sequencing [illegible] eam *Staphylococcus aureus* isolates does n[illegible]sh bacteraemia from endocarditis

Berit Lilje,[1] Rasmus Ve[illegible]ers Dahl,[2] Marc Stegger,[1] Robert Leo Skov,[1] Vance G. Fowler Jr,[3] Kim Lee Ng,[1] Kri[illegible]mod Larsen,[1] Andreas Petersen,[1] Helle Krogh Johansen,[4] Henrik Car[illegible]us Arpi,[6] Flemming S. Rosenvinge,[7] Eva Korup,[8] Ulla Høst,[2] Christian Hassager,[9] Sabine Ute A[illegible]omas Fritz Hansen,[2] Thor Bech Johannesen,[2] Jesper Smit,[11] Peter Søgaard,[12] Paal Skytt An[illegible],13,14,* and Niels Eske-Bruun[15]

Confirmed on 623 isolates

Phenotype ?

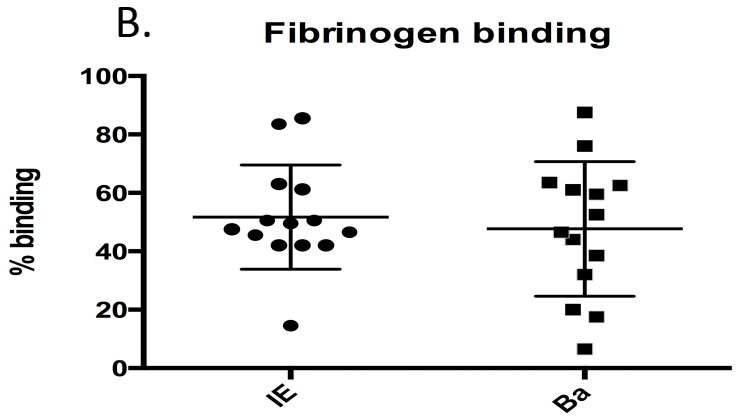
- Search for discriminant phenotype
- Based on previous in vitro evidences or animal studies..
- VIRSTA cohort: IE / non-IE Bacteremia isolates

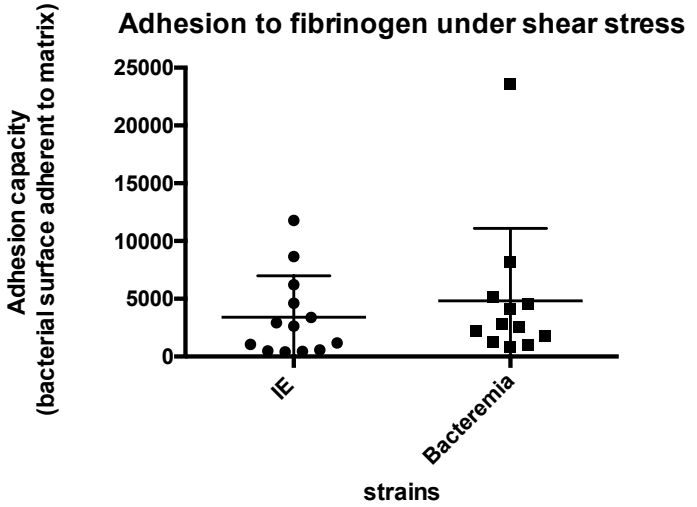
Phenotypes **(mean ± SD)**	IE (n=14)	Ba (n=14)	*P* [(a)]
Fibrinogen binding (% of binding)	51.7±10.22	47.7±10.14	0.611
Fibronectin binding (% of binding)	45.7±7.31	47.4±5.82	0.826
Endothelial cells adhesion (% of binding)	93.9 ±28.80	90.1 ±33.12	0.853
Endothelial cells internalization (% of internalization)	133.1 ±13.23	140.4 ±19.45	0.483
Biofilm production (BFI)	12.5±7.21	12.3±7.41	0.968
hNP-1 resistance (% of survival)	35.3±9.27	36.6±18.25	0.810
Staphylokinase production (kinetics slope)	0.13±0.031	0.21±0.045	0.130
Platelet aggregation (lag time)	2.5 ±2.42	2.2±1.57	0.757
CD69 activation (fluorescence intensity)	694.6 ±133.28	631.8 ±158.83	0.764

Phenotypes IE vs Bacteremia

Bouchiat, Inf Genet Evol 2015

Adhesion to Fg under shear stress

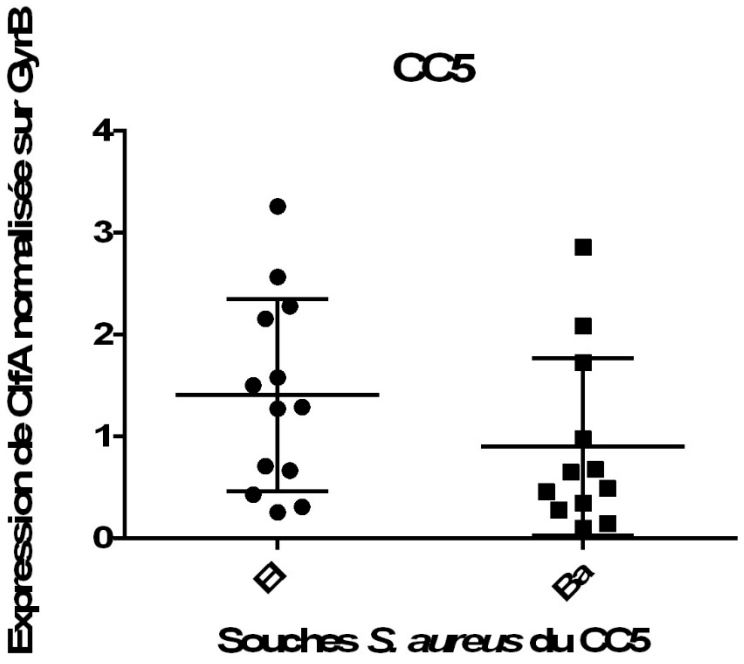




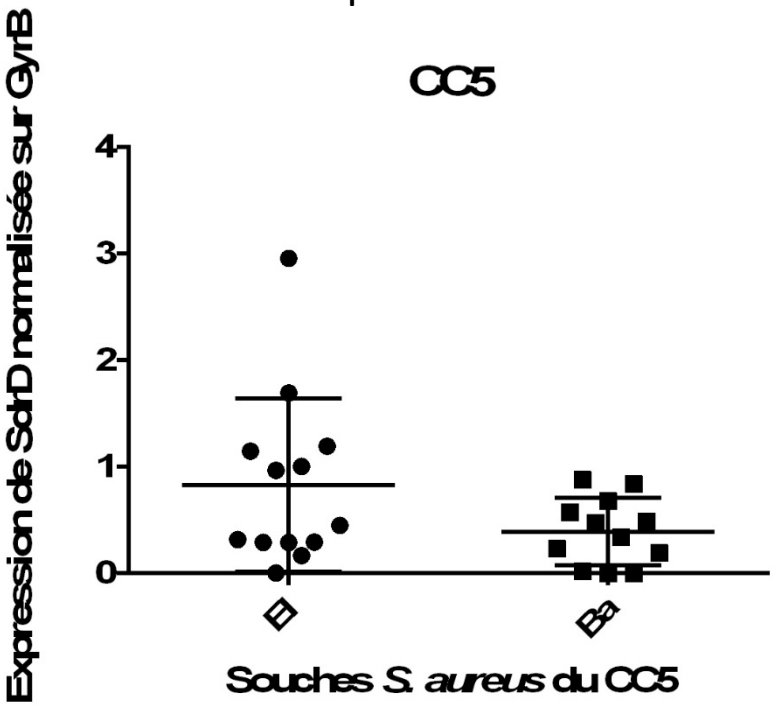
Bouchiat, Inf Genet Evol 2015 – Liesenborghs and Bouchiat, unpublished

Surface protein expression

qRT-PCR ClfA

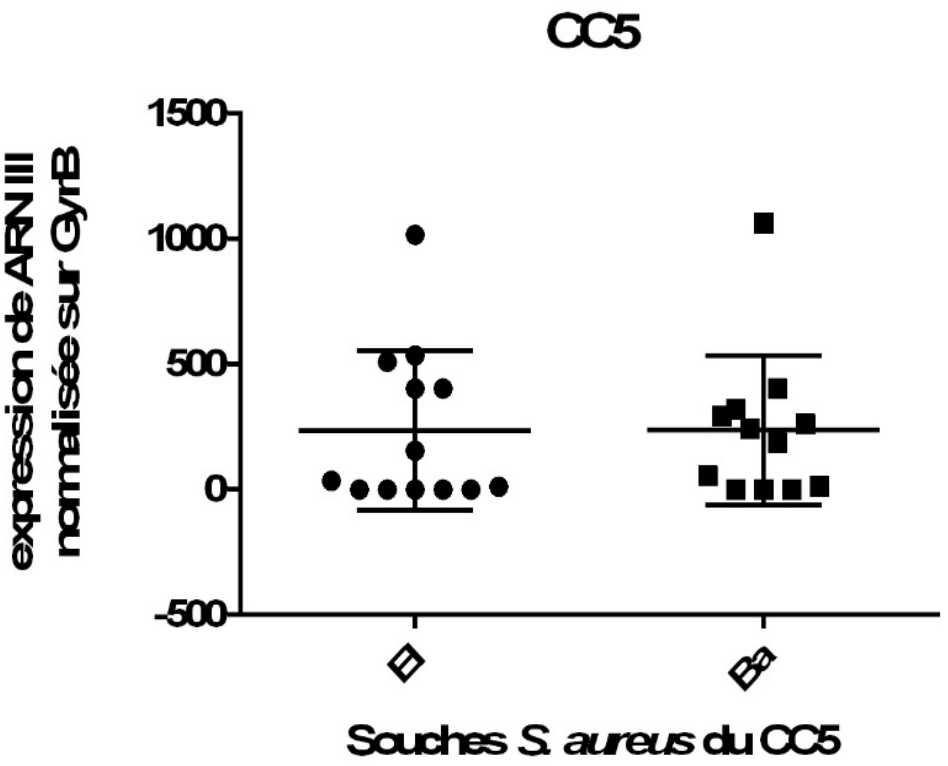


qRT-PCR SdrD



Tchikaya & Moreau unpublished

RNAIII expression

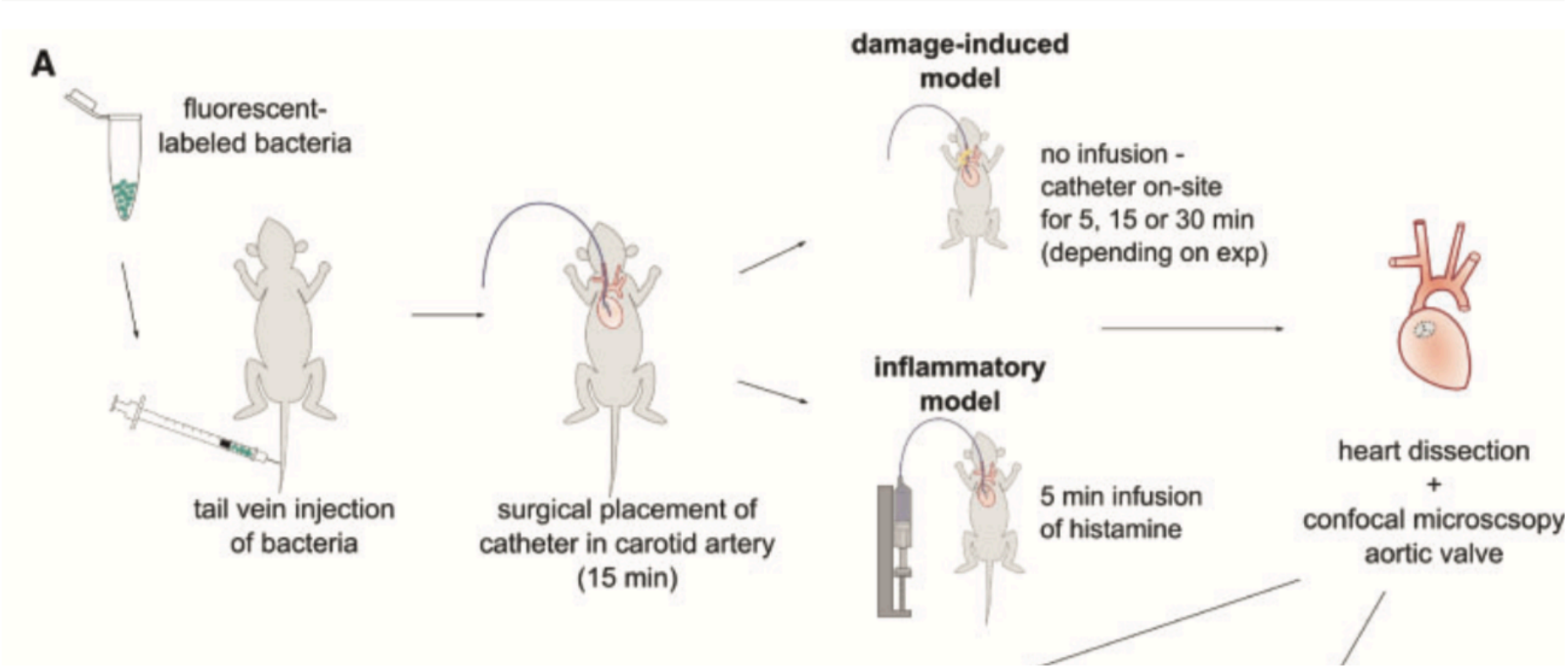


Tchikaya & Moreau unpublished

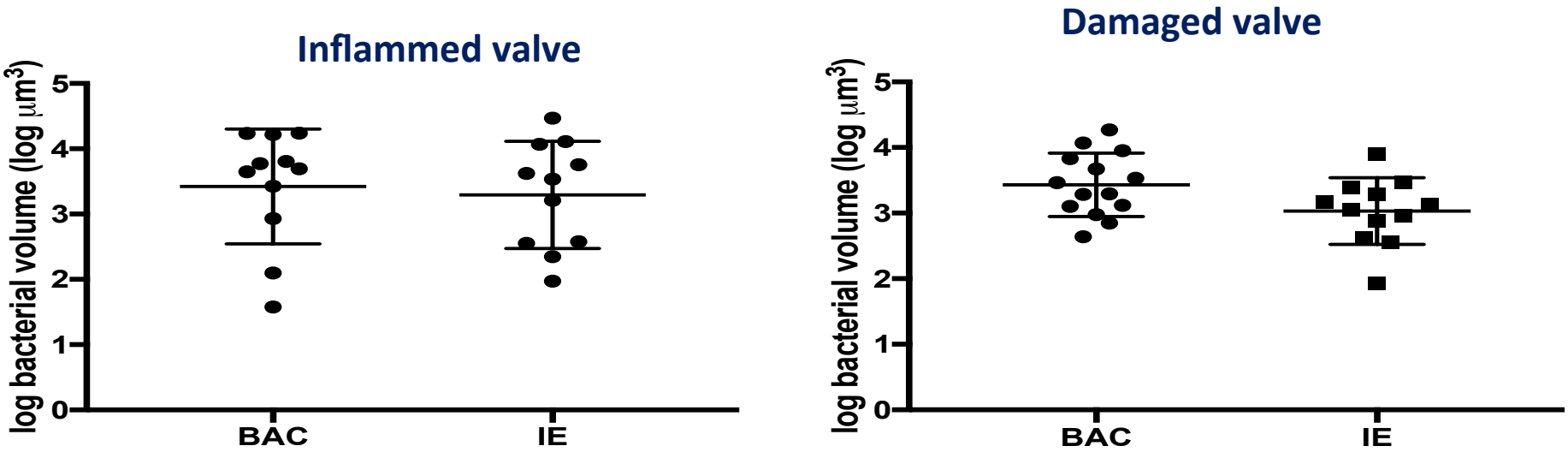
Phenotype ?

- No discriminant in vitro phenotype identified
- ? In vivo phenotype
  - > Animal models

The Leuven mice models



Adhesion on valves

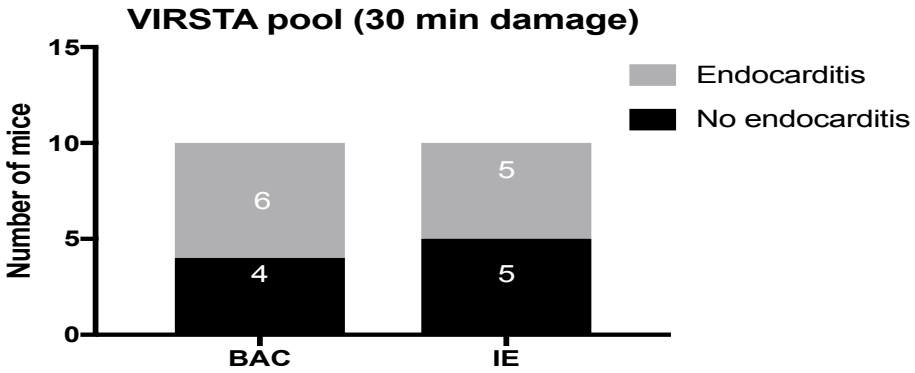


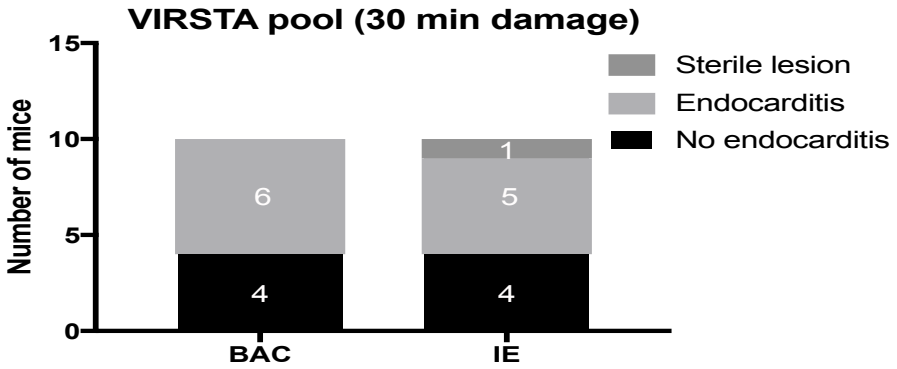
CC5 VIRSTA: 12 IE strains, 12 Bacteremia strains, 11 mices per group

Laurens Liesenborghs & Severien Meyers

No difference between the IE and BAC pool in damage induced endocarditis

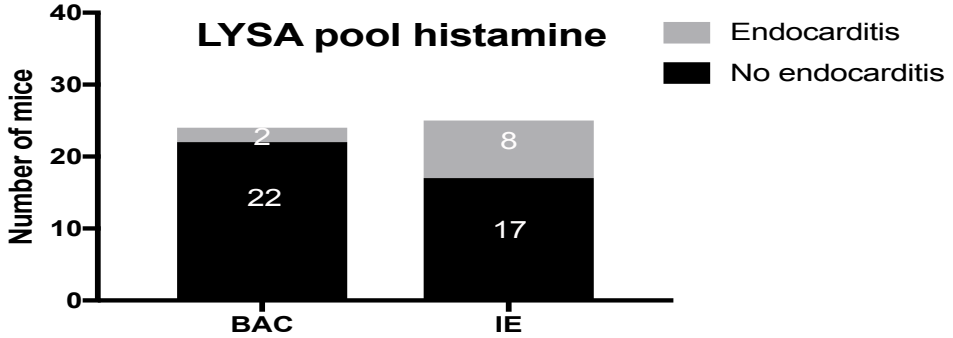
VIRSTA cohort CC5 (log 6)



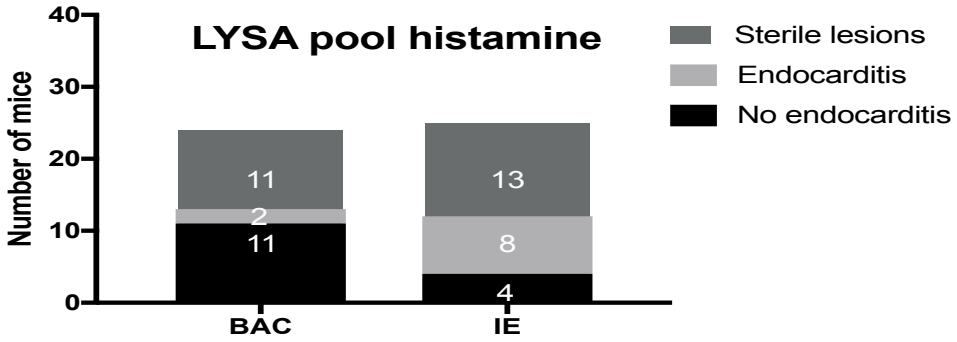


Laurens Liesenborghs & Severien Meyers

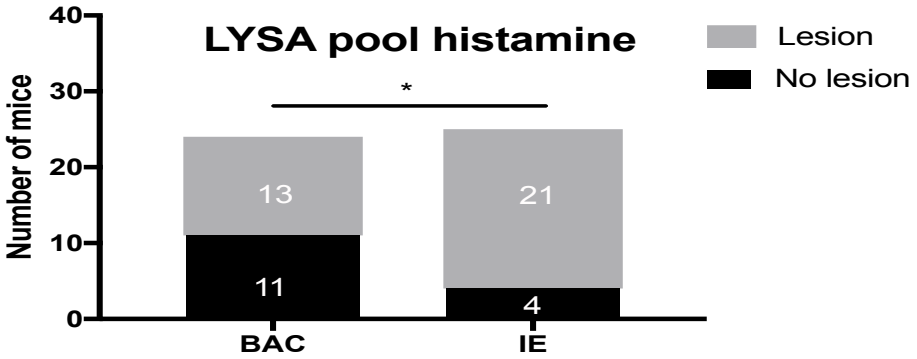
The CC5 IE pool MAY causes more lesions in the inflammatory model



P=0.0738



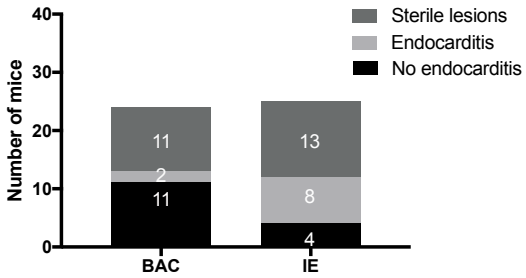
VIRSTA cohort CC5

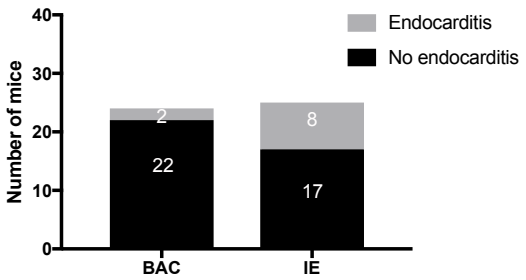


Laurens Liesenborghs & Severien Meyers

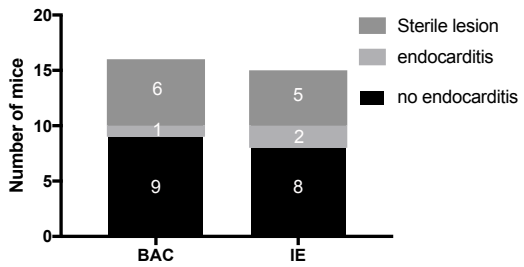
The CC5 IE pool but not CC45 pool causes more lesions in the inflammatory model

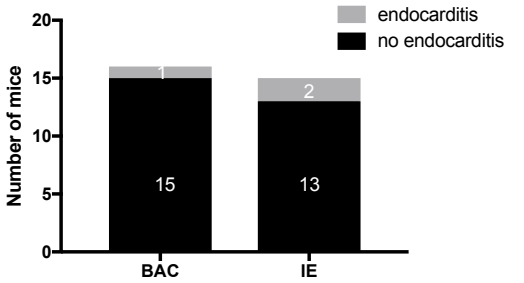
CC5



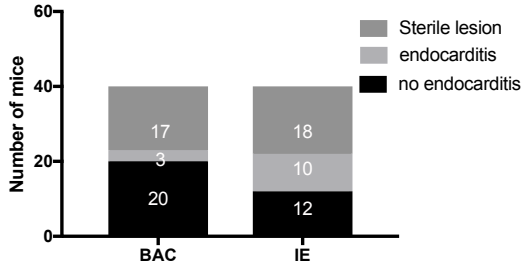


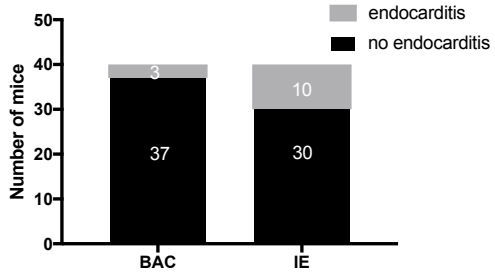
CC45





CC 5 + CC45





The bug: pathovars associated with IE ?

- No genomic signal on large cohorts
- No relevant in vitro phenotype identified
- Animal:
  - mechanical damage-induced IE model: no signal
  - inflammatory model of IE (relevance ++): weak signal

Factors affecting the occurrence of IE in the course of IE

- Predisposing factors: at risk cardiopathy, IV drug user, previous IE..
- The bug: pathovars associated with IE ?
- The host: genetic predisposition associated with IE ?

Predispositions to SA infections

Potential associations between common genetic variants and human susceptibility to *S. aureus* infection by GWAS:

- 361 AB vs 699 controls (Nelson, *BMC Infectious Diseases* 2014): NS
- 309 SA-infected people vs 2952 controls (Ye, *Front Genet* 2014): NS
- GWAS evidence of human genetic susceptibility to *S. aureus* infection: 4701 case of *S.aureus* infections and 45344 controls. Two polymorphisms located near HLA-DRA and HLA-DRB1 genes on chromosome 6 in the HLA class II region achieved genome-wide significance. (DeLorenze, JID 2016).
- HLA class II region on chromosome 6 associated with SAB susceptibility. 390 SAB, 175 controls. (Cyr, Genes Immun 2017)

No study searched for the occurrence of IE in the course of *S.aureus* Bacteremia

Genome-wide association study on *Staphylococcus aureus*-induced endocarditis: Results from the VIRSTA cohort

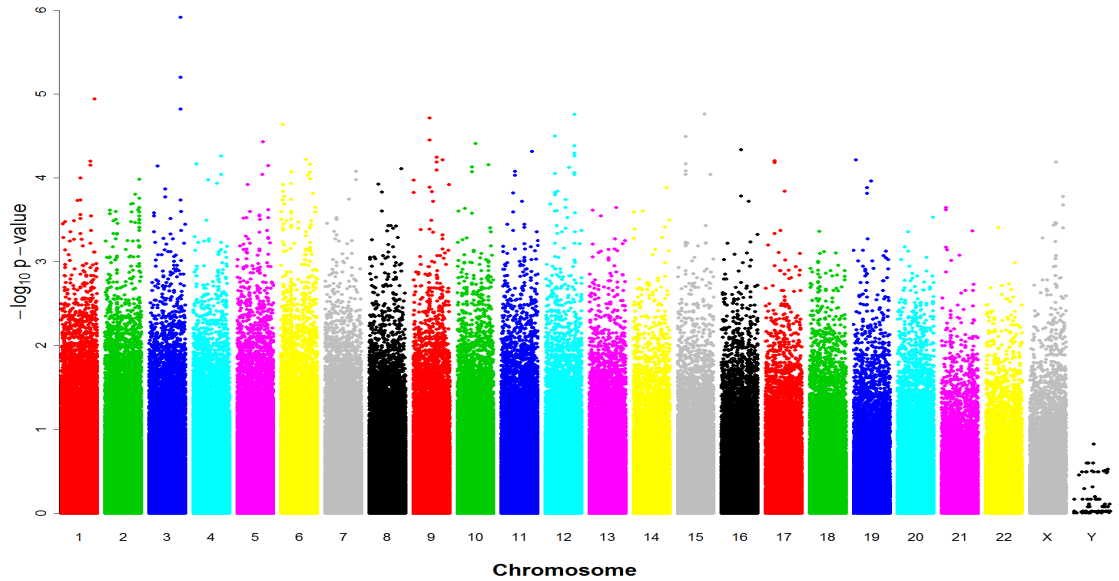
- VIRSTA study group and:
- Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada.
- Département de médecine moléculaire, Université Laval, Québec, Canada.
- Genetic Laboratory Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
- Statens Serum Institut, Copenhagen, Denmark

GWAS of IE: M&M

- Training cohort=Virsta
  - 78 patients presenting definite IE
  - 78 age- and gender-matched control SAB patients
- Replication sets=Danish cohort
  - 57 patients presenting IE
  - 153 patients presenting non-IE bacteremia
- Genotyping
    - Illumina HumanOmni Exp-12v1 BeadChip array

Moreau, Front Microbiol 2018

Manhattan plot – GWAS VIRSTA cohort



Three nominally associated SNPs (p-value < 1x10-5) were identified on chromosome 3

Moreau, Front Microbiol 2018

GWAS VIRSTA cohort

- The 3 SNPs (p-value < 1x10-5) on chromosome 3 were near or within the genes CLDN11 and SLC7A14
- Frequency of the minor allele lower in cases than in controls
  - > suggest a protective effect of the minor allele against IE

SNP	Chromosome	Position on Hg19	A1/A2	A1 in cases	A1 in controls	OR	P-value	Position to SLC7A14gene	Position to CLDN11 gene
rs6414536	3	170176173	A / G	0.127	0.361	0.257	6.248e-06	-	Intron
rs2287489	3	170178057	A / C	0.127	0.361	0.257	6.248e-06	3' UTR	Intron
rs4955730	3	170179621	G / A	0.112	0.361	0.223	1.212e-06	3' UTR	Intron
rs6769887	3	170172774	G / A	0.082	0.285	0.225	1.496e-05	-	Intron

Moreau, Front Microbiol 2018

Replication set: Danish patients

- 57 cases and 153 controls
- Study limited to the best 2 candidates
- PCR-sequencing on those 2 loci
- -> Although non-significant, the frequency of the minor allele is lower in cases than in Bacteremia
- -> suggest a protective effect of the minor allele against IE

SNP	A1/A2	A1 in 57 SaEI Cases	A1 in 153 controls	OR	P value
rs2287489	A/C	0.2946	0.3208	0.8843	0.6215
rs4955730	G/A	0.2797	0.3171	0.8362	0.468

Moreau, Front Microbiol 2018

Expression Quantitative Trait Loci

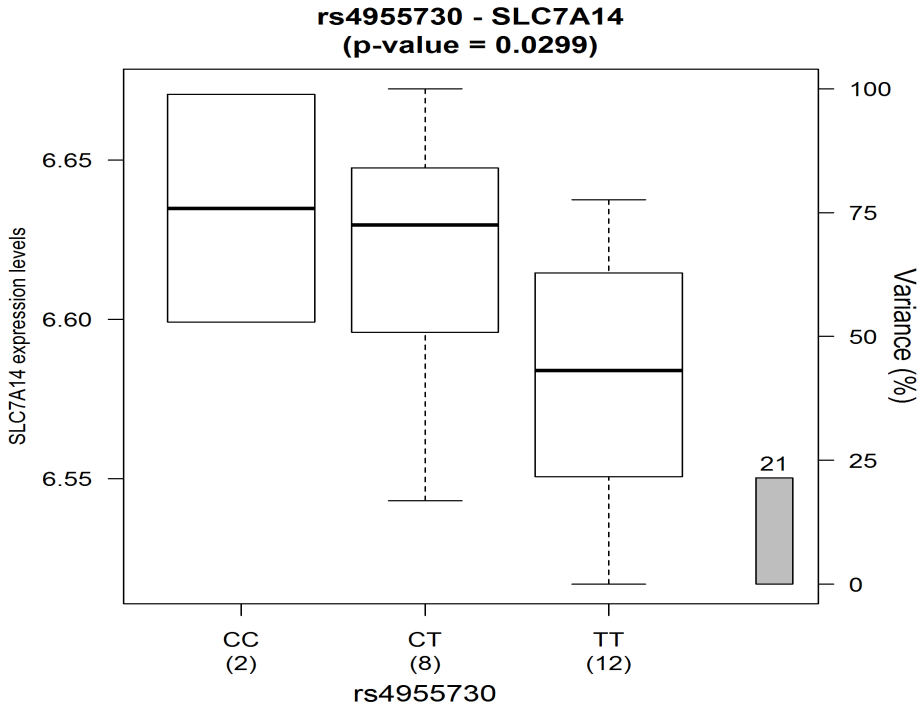
- functional meaning of nominated SNPs assessed by quantification of mRNA expression
- Material: explanted aortic valves from patients with calcific stenosis
- RNA expression on Illumina expression BeadChips
- Results:
  - No SNPs associated with the expression of CLDN11
  - Significant association for SLCA14 (unknown function)

Moreau, Front Microbiol 2018

Valve eQTL

(Expression Quantitative Trait Loci)

- Allele rs4955730-C associated with increased mRNA levels of SLC7A14 in aortic valve tissues.
- Tentative model: the minor allele decreases susceptibility to IE through up-regulation of SLC7A14 in valve tissue



Moreau, Front Microbiol 2018

The occurrence of IE in human: a tentative model

- Most human are genetically susceptible to IE, a fraction harbour SNPs that maybe protective. Larger cohort needed
- Most *S.aureus* can cause IE, if some alteration is important, they are unique (strain-specific) and undetectable by GWAS unless hundred thousand isolates are tested
- > very large (100 000) international cohort needed

Virsta study group

(Vincent Le Moing)

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Sponsor CHU de Montpellier: Sandrine Barbas, Christine Delonca, Virginie Sussmuth, Anne Verchère.

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- Duke University: Vance Fowler
- Pasteur Institute. Sylvain Brisse, Philippe Glaser

Human susceptibility
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- Institut universitaire de cardiologie et de pneumologie de Québec : Alison Clémenceau
- Cardiology Department, AP-HP, Bichat Hospital, Paris, France: David Messika-Zeitoun
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- The VIRSTA Study group Xavier Duval & Vincent Le Moing

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ciri Centre International de Recherche en Infectiologie

STAPHYLOCOQUES Centre National de Référence

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- Patricia Simoes-Martin
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