The Future Of *Staphylococcus aureus* Bacteremia And Endocarditis: From Biofilm Eradication To Artificial Intelligence

Vance G. Fowler, Jr, MD, MHS

Disclosures

Nature of Relevant Financial Relationship	Commercial Interest
Grant or research support	Cerexa/Actavis, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Cubist/Merck; Karius; Contrafect; Genentech; Regeneron
Paid consultant	Achaogen, Astellas, Arsanis; Affinergy; Basilea; Bayer; Cerexa, Contrafect; Cubist;Debiopharm, Destiny; Genentech/Roche; Integrated Biotherapeutics; MedImmune; Novartis, Theravance; Brii, Affinivax, Armata, ArcBio, Akagera, Aridis, Synermore,Zymeron
Speaker's Bureau	None
Employment	Duke University
Stock options	ArcBio, Valanbio
Other relevant financial interests	Patent pending in sepsis diagnostic, Predigen, Inc.
Royalties	UptoDate
Honoraria	IDSA for Assoc. Editor role, *Clinical Infectious Diseases*

S. aureus Bacteremia and IE

- Where were we?
- Where are we?
- Where are we going?

S. aureus Bacteremia and IE

- Where were we?
- Where are we?
- Where are we going?

Fifteen Years' Experience with Staphylococcus Septicemia in a Large City Hospital*

Analysis of Fifty-five Cases in the Cincinnati General Hospital 1940 to 1954

RODMAN WILSON, M.D. *and* MORTON HAMBURGER, M.D.
Cincinnati, Ohio

AMERICAN JOURNAL OF MEDICINE MARCH, 1957

TABLE I

INCIDENCE, INCIDENCE OF ENDOCARDITIS AND MORTALITY RATE OF STAPHYLOCOCCAL SEPTICEMIA AT THE CINCINNATI GENERAL HOSPITAL, 1940–1954

Year	Cases	Cases of Endocarditis	Deaths
1940 *	2	1	2
1941	3	1	2
1942	5	4	5
1943	3	3	3
1944	7	4	4
1945	0	. .	. .
1946	1	0	1
1947	2	2	2
1948	3	1	1
1949	4	2	2
1950	6	4	4
1951	8	6	7
1952	3	1	2
1953	5	5	2
1954	3	1	2
Totals	55	35 (64%)	39 (71%)

* Incomplete year

CLINICAL PROGRESS

Circulation, Volume XIX, March 1959

Staphylococcal Bacteremia and Endocarditis

By RICHARD H. MEADE, III, M.D.

TABLE 1.—*Origins of Staphylococcal Bacteremia*

Years	1936-1942 (References 22, 29, 40)		1952-1957 (References 2, 18, 21, 31, 33, 41, 42)	
Number of cases	238		258	
Predisposing factors	No.	%	No.	%
1. Infection				
Skin	91	38.2	37	14.3
Respiratory tract	25	10.5	17	6.6
Mastoid	3	1.3	3	1.2
Bone	40	16.8	6	2.4
Urinary tract	15	6.3	13	5.0
Genital tract	7	2.9	17	6.6
Bowel	1	0.4	6	2.4
Teeth	3	1.2	8	3.2
Lymph node	1	0.4	1	0.4
Joints	1	0.4	1	0.4
Veins				
Cannula	1	0.4	3	1.2
Drug addiction			2	0.8
Septic phlebitis			2	0.8
2. Postoperative complications				
Surface wound infection	15	6.3	7	2.8
Respiratory tract			5	2.0
Genito-urinary tract			7	2.8
Prostate			31	12.0
Bone	4	1.6	6	2.4
Central nervous system			1	0.4
3. Undetermined	31	13.0	36	14.0
4. Undetermined but associated with other disease			47	18.2

S. aureus Bacteremia and IE

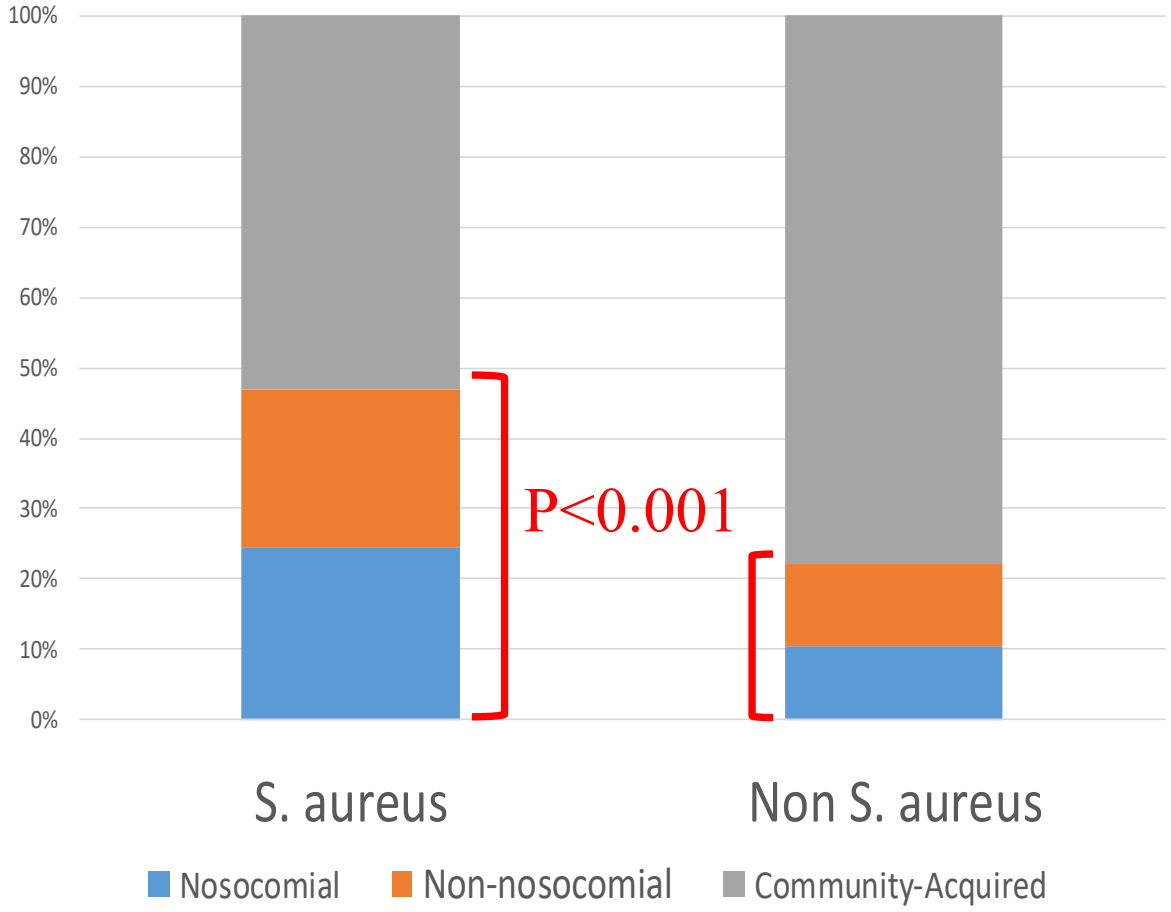
- Where were we?
- Where are we?
- Where are we going?

Staphylococcus aureus Endocarditis

A Consequence of Medical Progress

Vance G. Fowler, Jr, MD, MHS
Jose M. Miro, MD, PhD
Bruno Hoen, MD, PhD
Christopher H. Cabell, MD, MHS
Elias Abrutyn, MD
Ethan Rubinstein, MD, LLb
G. Ralph Corey, MD
Denis Spelman, MD
Suzanne F. Bradley, MD
Bruno Barsic, MD, PhD
Paul A. Pappas, MS
Kevin J. Anstrom, PhD
Dannah Wray, MD
Claudio Q. Fortes, MD
Ignasi Anguera, MD
Eugene Athan, MD
Philip Jones, MD
Jan T. M. van der Meer, MD
Tom S. J. Elliott, PhD, DSc FRCPath
Donald P. Levine, MD
Arnold S. Bayer, MD
for the ICE Investigators

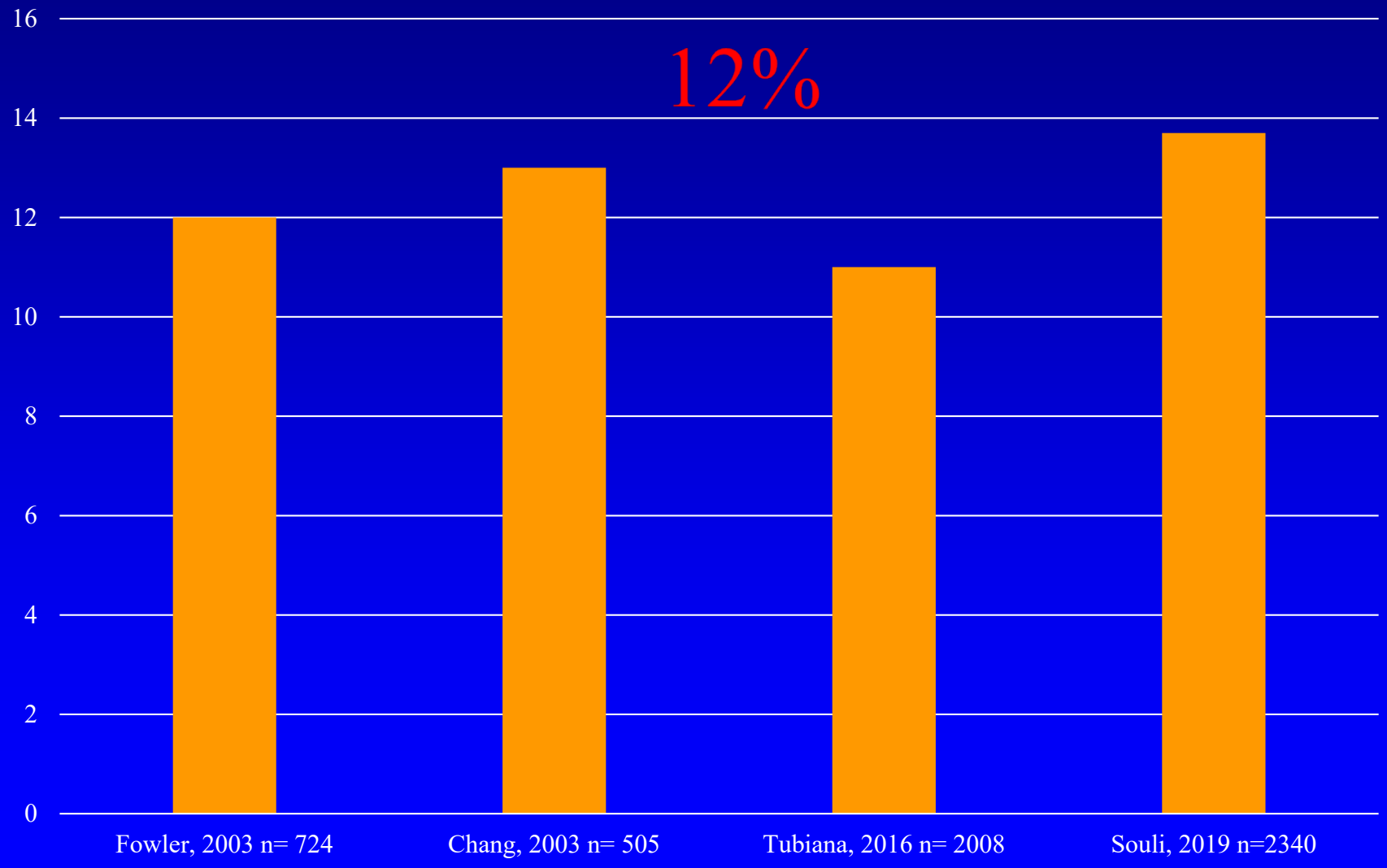
S. aureus IE is Healthcare-Associated



JAMA. 2005;293:3012-3021.

Risk of Endocarditis in Patients with SAB?

>4800 prospectively enrolled patients with SAB



Clinical Infectious Diseases

MAJOR ARTICLE

Changing Characteristics of *Staphylococcus aureus* Bacteremia: Results From a 21-Year, Prospective, Longitudinal Study

Maria Souli,[1,2,3] Felicia Ruffin,[1] Seong-Ho Choi,[1,4] Lawrence P. Park,[1,5] Shengli Gao,[1,6] Nicholas Christopoulos Lent,[1] Batu K. Sharma-Kuinkel,[1] Joshua T. Thaden,[1] Stacey A. Maskarinec,[1] Lisa Wanda,[1,7] Jonathan Hill-Rorie,[1,8] Bobby Warren,[1] Brenda Hansen,[1,9] and Vance G. Fowler Jr[1,2]

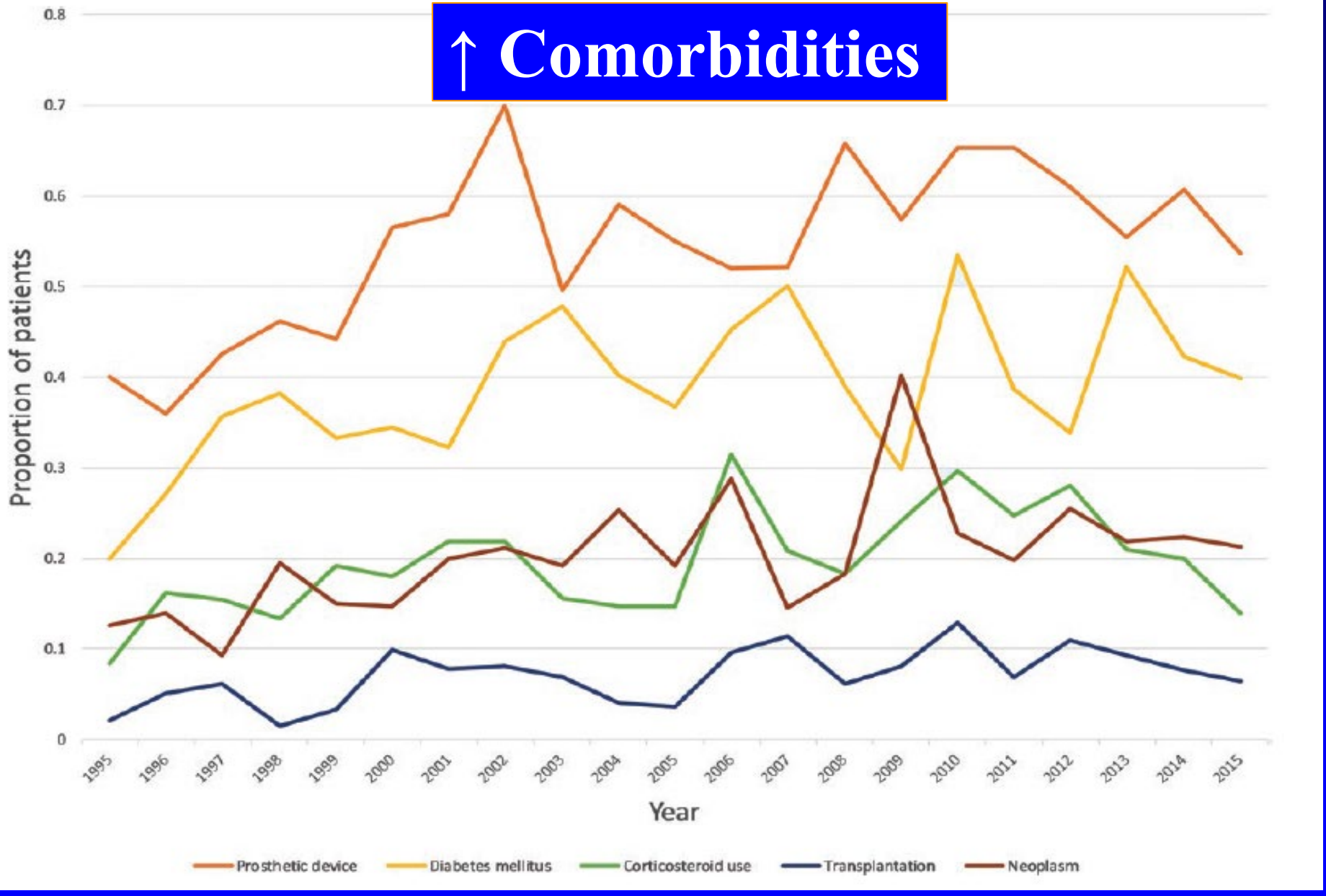
[1]Department of Medicine, Duke University Medical Center and [2]Duke Clinical Research Institute, Durham, North Carolina; [3]Fourth Department of Internal Medicine, National and Kapodistrian University of Athens School of Medicine, Greece; [4]Department of Internal Medicine, Division of Infectious Diseases, Chung-Ang University College of Medicine, Seoul, South Korea; [5]Duke Global Health Institute, Duke University, Durham, North Carolina; [6]The First People's Hospital of Wujiang District, Suzhou City, Jiangsu Province, China; [7]School of Medicine, University of North Carolina, Chapel Hill; [8]Harvard T. H. Chan School of Public Health, Boston, Massachusetts; and [9]Pediatric Gastroenterology, University of North Carolina, Chapel Hill.

Clinical Infectious Diseases® 2019;69(11):1868–77

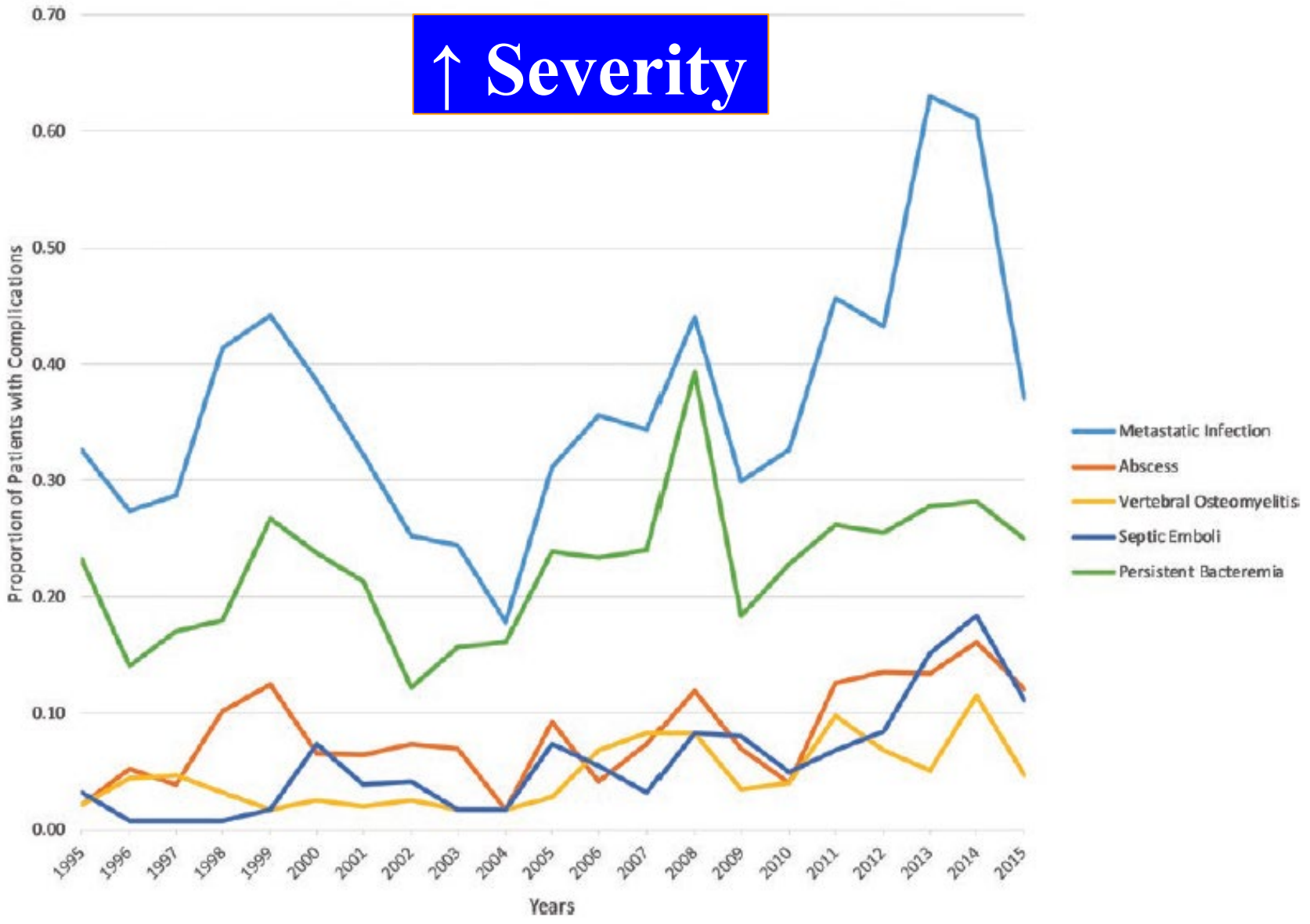
- ~2400 Prospectively enrolled patients with SAB at Duke
- Continuous enrollment 1994-2015
- *Spa* typing on all 2400 isolates

- Three questions:
  - *1) Did clinical phenotype of SAB change over study period?*
  - *2) Did bacterial genotype of SAB change over study period?*
  - *3) Are clinical phenotype and bacterial genotype related?*

↑ Comorbidities



↑ Severity


0.70
0.60
0.50
0.40
0.30
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Proportion of Patients with Complications
1995
1996
1997
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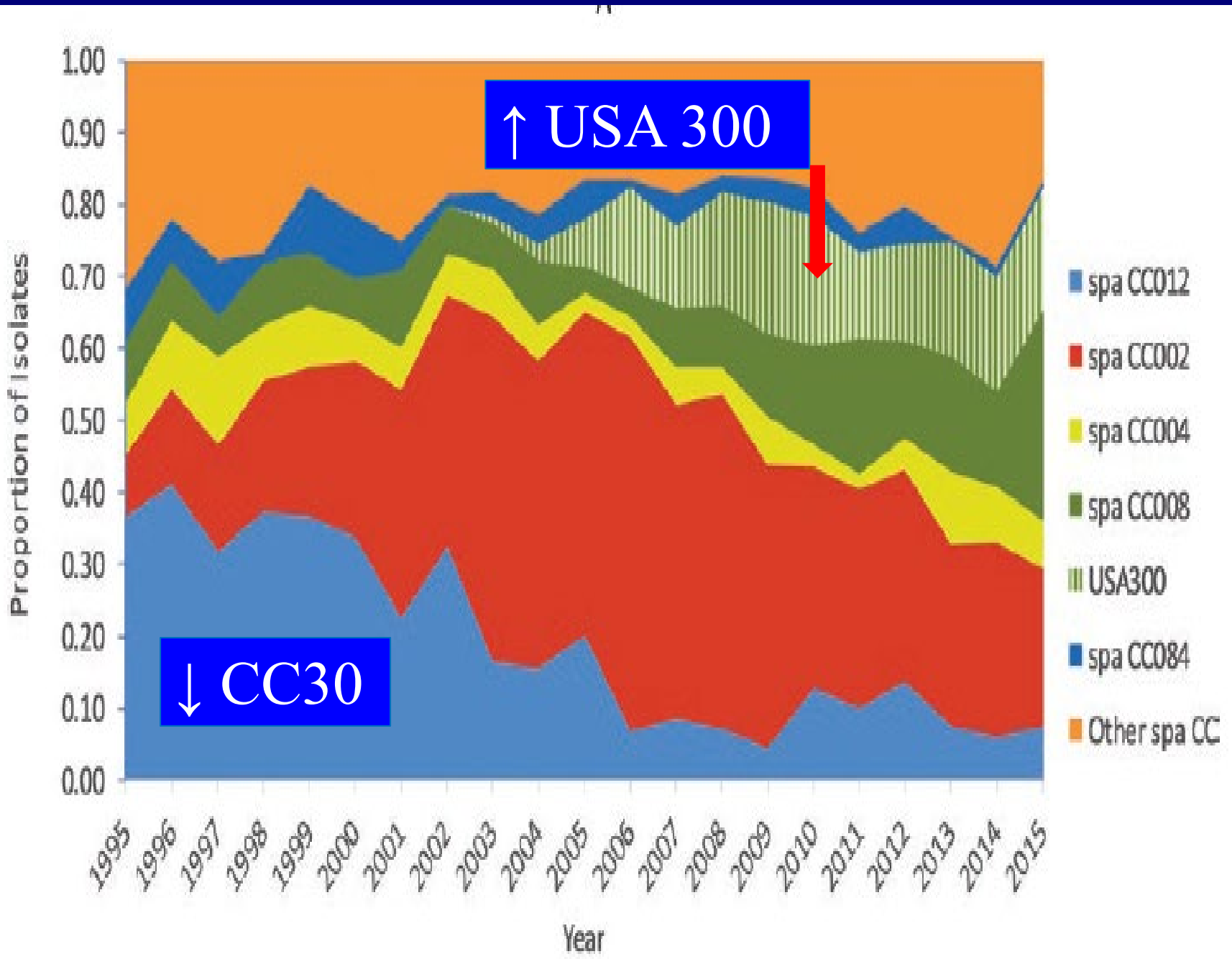
Years
Metastatic Infection
Abscess
Vertebral Osteomyelitis
Septic Emboli
Persistent Bacteremia


↑ USA 300
↓ CC30
Proportion of Isolates
1.00
0.90
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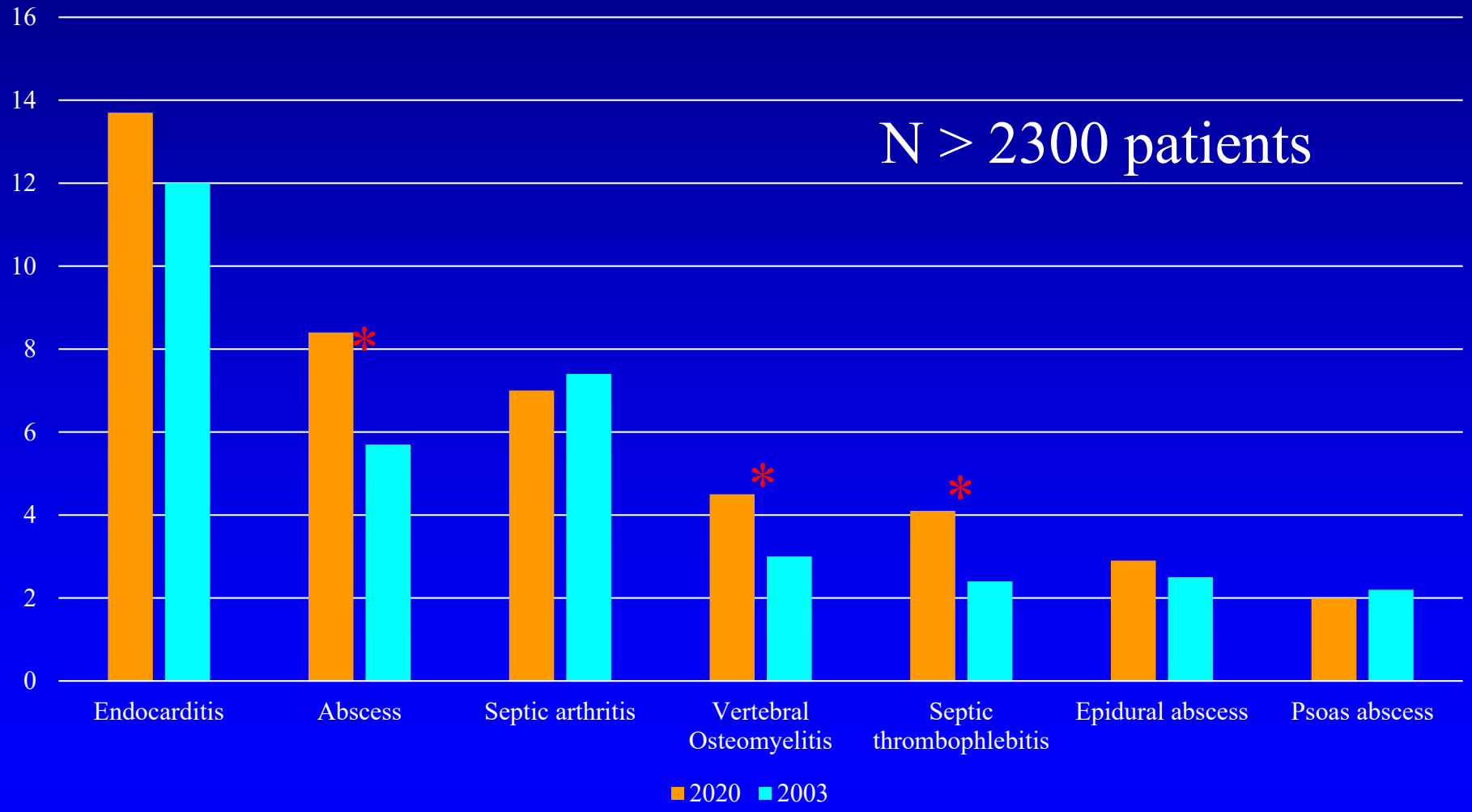
Year
spa CC012
spa CC002
spa CC004
spa CC008
USA300
spa CC084
Other spa CC

USA300 Associated with Increased Severity of Infection

	Metastatic Complications	Abscess	Emboli	Persistent Bacteremia
Variable		OR (95% CI)		
Genotype				
All genotypes except *spa*-CC008	Reference			
spa-CC008 non-USA300	1.17 (.87–1.56)	1.41 (.89–2.22)	0.98 (.55–1.77)	1.17 (.84–1.63)
USA300	**1.42 (1.02–1.99)**[a]	1.52 (.93–2.46)	**2.05 (1.20–3.48)**[b]	**1.95 (1.38–2.78)**[b]

Risk of Abscess, but not Endocarditis, Increased in Patients with SAB in Past 2 Decades



* $p < 0.01$ overall trend

Clinical Infectious Diseases® 2019;69(11):1868–77

S. aureus Clonal Variation is Associated with Endocarditis

Category, clonal complex	Isolates, no.	Nasal carriage only	Uncomplicated infection	Bacteremia with hematogenous complications	*P*[a]
Both MRSA and MSSA (n = 371)					
1	32	12 (38)	11 (34)	9 (28)	.1763
5	84	21 (25)	13 (15)	50 (60)	.0025
8	44	16 (36)	15 (34)	13 (30)	.1612
9	11	2 (18)	1 (9)	8 (73)	.0764
15	20	10 (50)	7 (35)	3 (15)	.0146
30	96	22 (23)	27 (28)	47 (49)	.0308
45	31	11 (35)	8 (26)	12 (39)	.6431
59	11	4 (36)	3 (28)	4 (36)	.6917
All not common	42	18 (43)	17 (40)	7 (17)	NA
Total	371	116 (31)	102 (28)	153 (41)	

Fowler et al. *J Infect Dis* **2007**; 196:738-47.

Clonal complex, no. (%)	Infective endocarditis (n = 113)	Soft tissue infection (n = 113)	*P* value
CC1	7 (6.2)	10 (8.8)	.615
CC5	14 (12.4)	6 (5.3)	.099
CC8	9 (8)	16 (14.2)	.203
CC15	15 (13.3)	10 (8.8)	.397
CC30	22 (19.5)	7 (6.2)	.005
CC45	16 (14.2)	25 (22.1)	.167
Other	30 (26.5)	39 (34.5)	.248

Nienaber et al. *J Infect Dis* **2011**; 204:704-13.

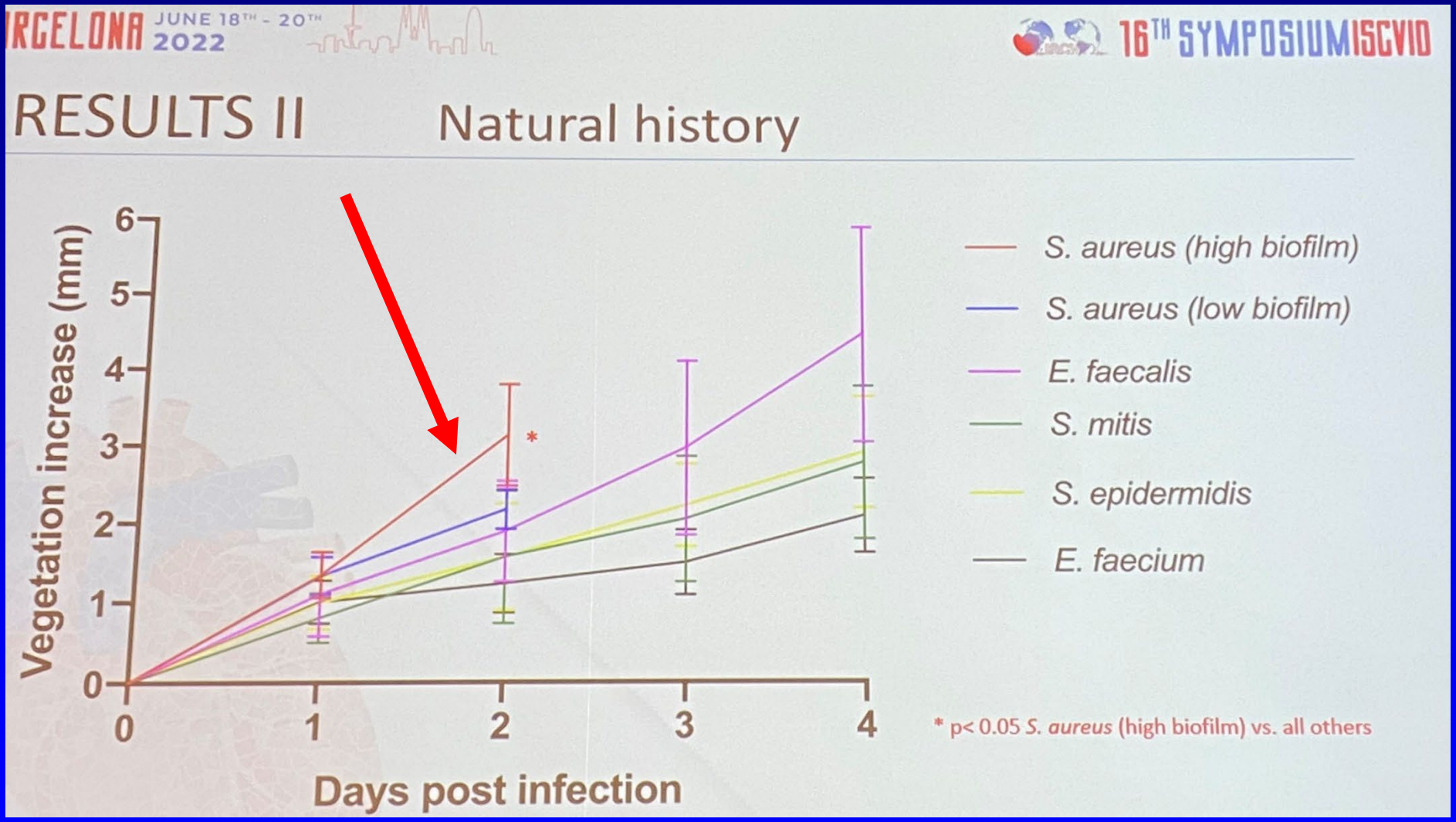
Comparison of *Staphylococcus aureus* strains for ability to cause infective endocarditis and lethal sepsis in rabbits

*Adam R. Spaulding[1], Erin A. Satterwhite[2], Ying-Chi Lin[3], Olivia N. Chuang-Smith[4], Kristi L. Frank[4], Joseph A. Merriman[1], Matthew M. Schaefers[3], Jeremy M. Yarwood[5], Marnie L. Peterson[3] and Patrick M. Schlievert[1]**

	IE	Sepsis
USA 200 (CC30)	+++	+
USA300 (CC8)	+	+++
USA (400)	+++	+++

Frontiers in Cellular and Infection Microbiology 2012; 2, 18: 1-9

CC30 Distinct IE Phenotype



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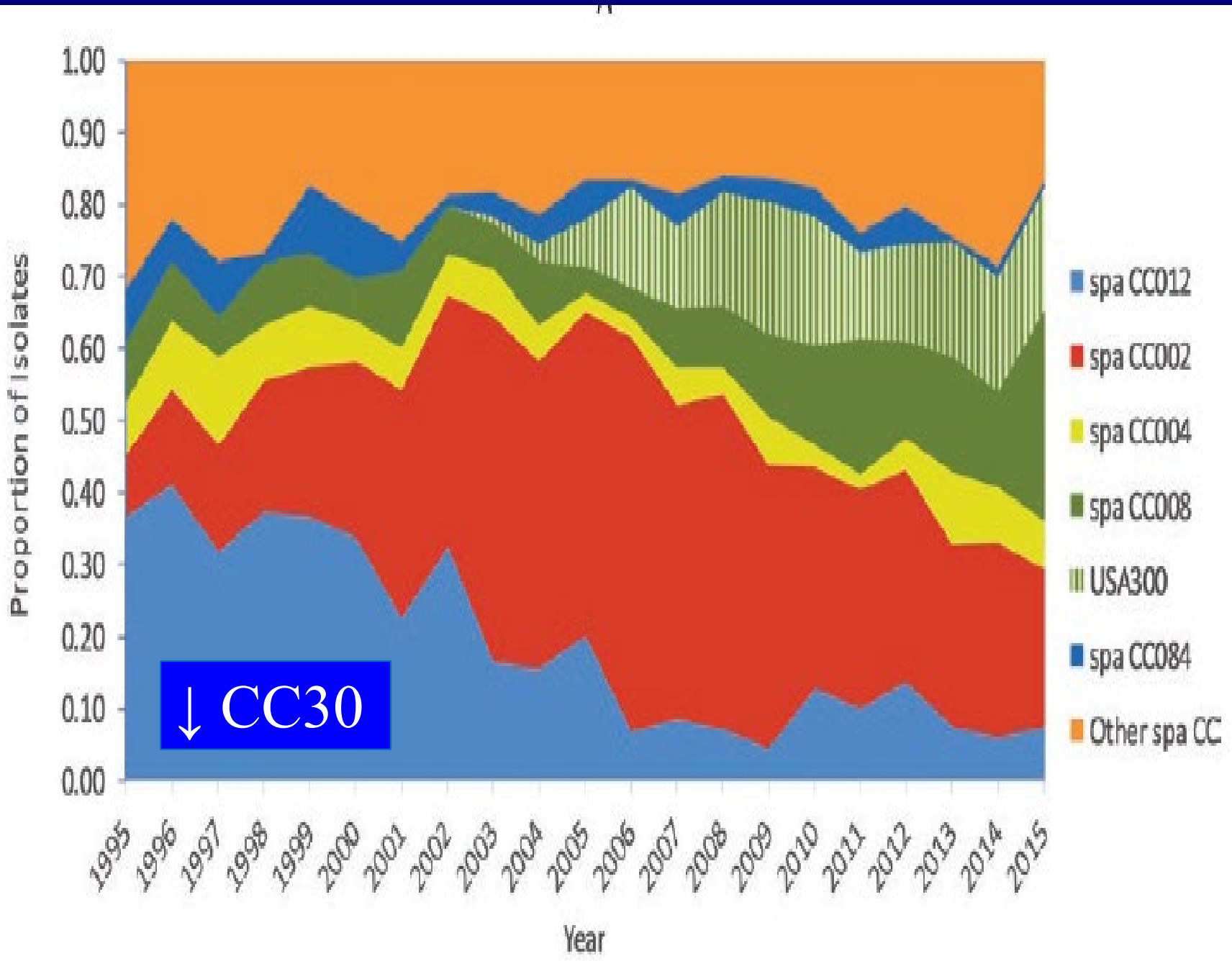
Proportion of Isolates
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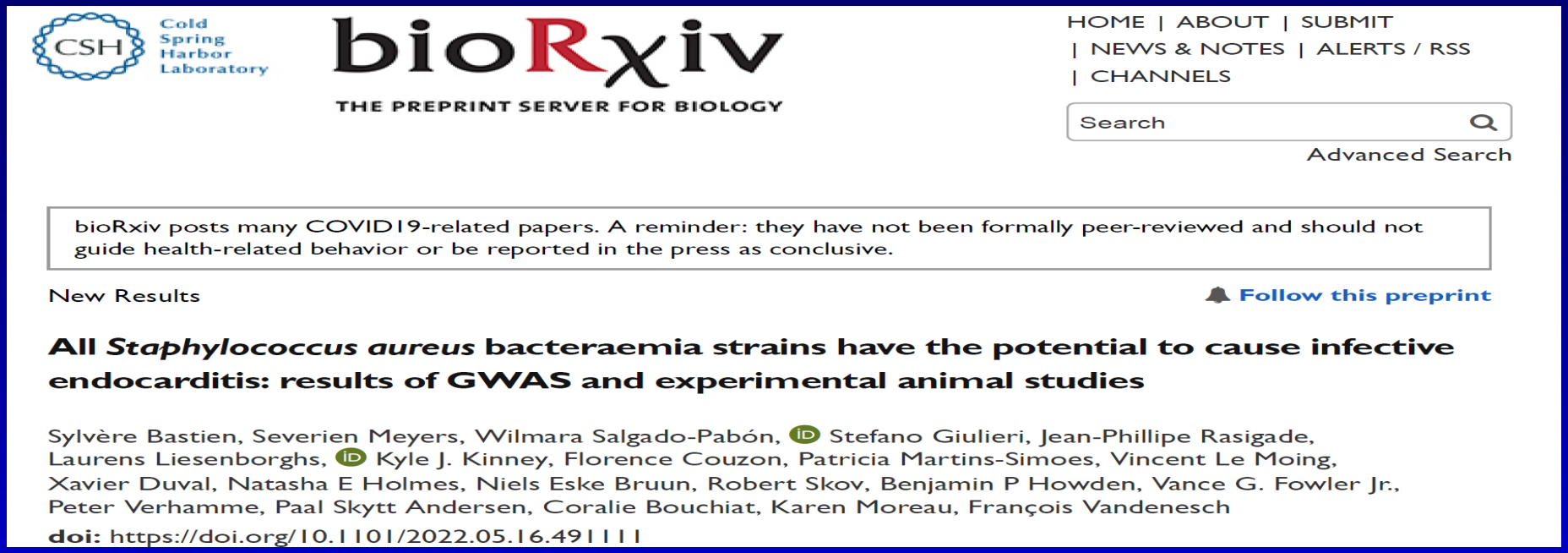
spa CC084
Other spa CC
↓ CC30



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bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

Follow this preprint

All *Staphylococcus aureus* bacteraemia strains have the potential to cause infective endocarditis: results of GWAS and experimental animal studies

Sylvère Bastien, Severien Meyers, Wilmara Salgado-Pabón, Stefano Giulieri, Jean-Phillipe Rasigade, Laurens Liesenborghs, Kyle J. Kinney, Florence Couzon, Patricia Martins-Simoes, Vincent Le Moing, Xavier Duval, Natasha E Holmes, Niels Eske Bruun, Robert Skov, Benjamin P Howden, Vance G. Fowler Jr., Peter Verhamme, Paal Skytt Andersen, Coralie Bouchiat, Karen Moreau, François Vandenesch

doi: https://doi.org/10.1101/2022.05.16.491111

- **GWAS Bloodstream Isolate (IE= 274, SAB= 650)**
  - *No difference by SNP, coding sequence, k-mer*
- **2 *in vivo* endocarditis models (mouse, rabbit)**
  - *No difference in valve adhesion, propensity to cause IE, vegetation size or CFU.*

Summary: SAB & IE

1) Patients changed: ↑ comorbidities

> ½ have prosthetic device

2) Severity changed: ↑ Metastatic infection

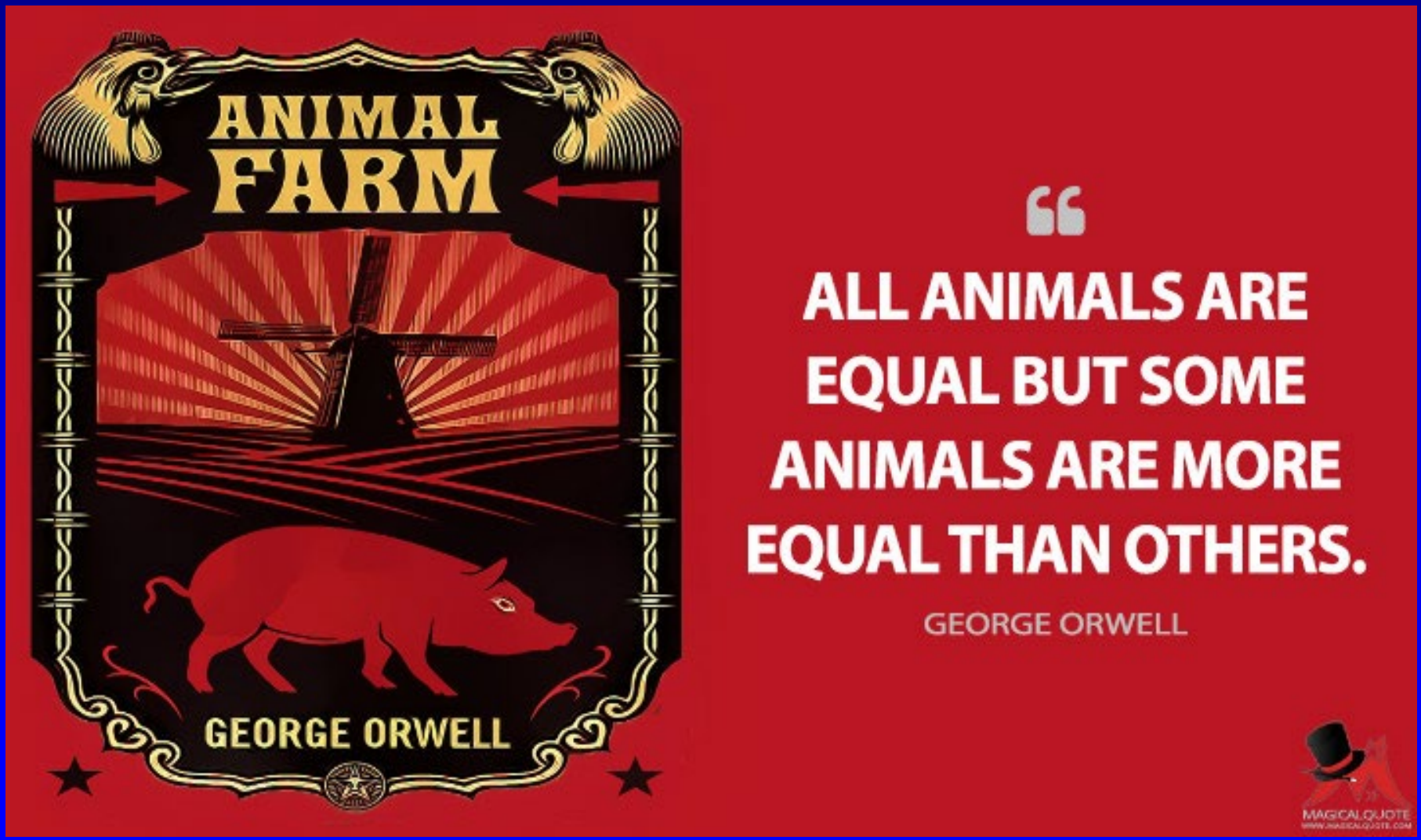
3) Bacteria changed:

↑ USA300 causing Bacteremia

↑ metastatic infection asstd with ↑ USA300

4) Bacterial Genotype and endocarditis…

S. aureus Genotype and IE



S. aureus Bacteremia and IE

- Where were we?
- Where are we?
- Where are we going?

Future of *S. aureus* Bacteremia & IE

Clinical Trials

Diagnostics

Biofilm

Machine Learning

Future of *S. aureus* Bacteremia & IE

Clinical Trials

Diagnostics

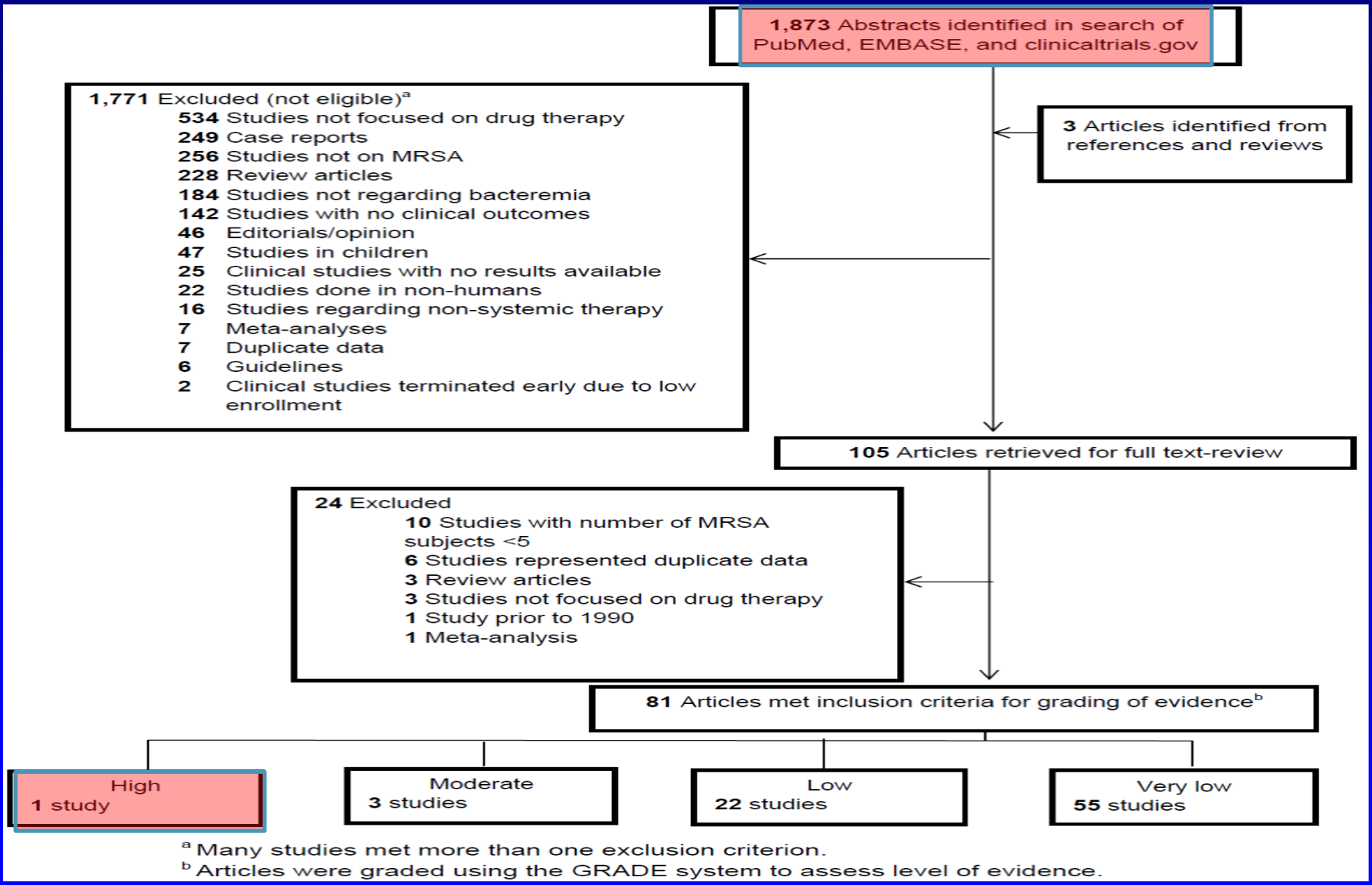
Biofilm

Machine Learning

Clinical Management of *Staphylococcus aureus* Bacteremia
A Review

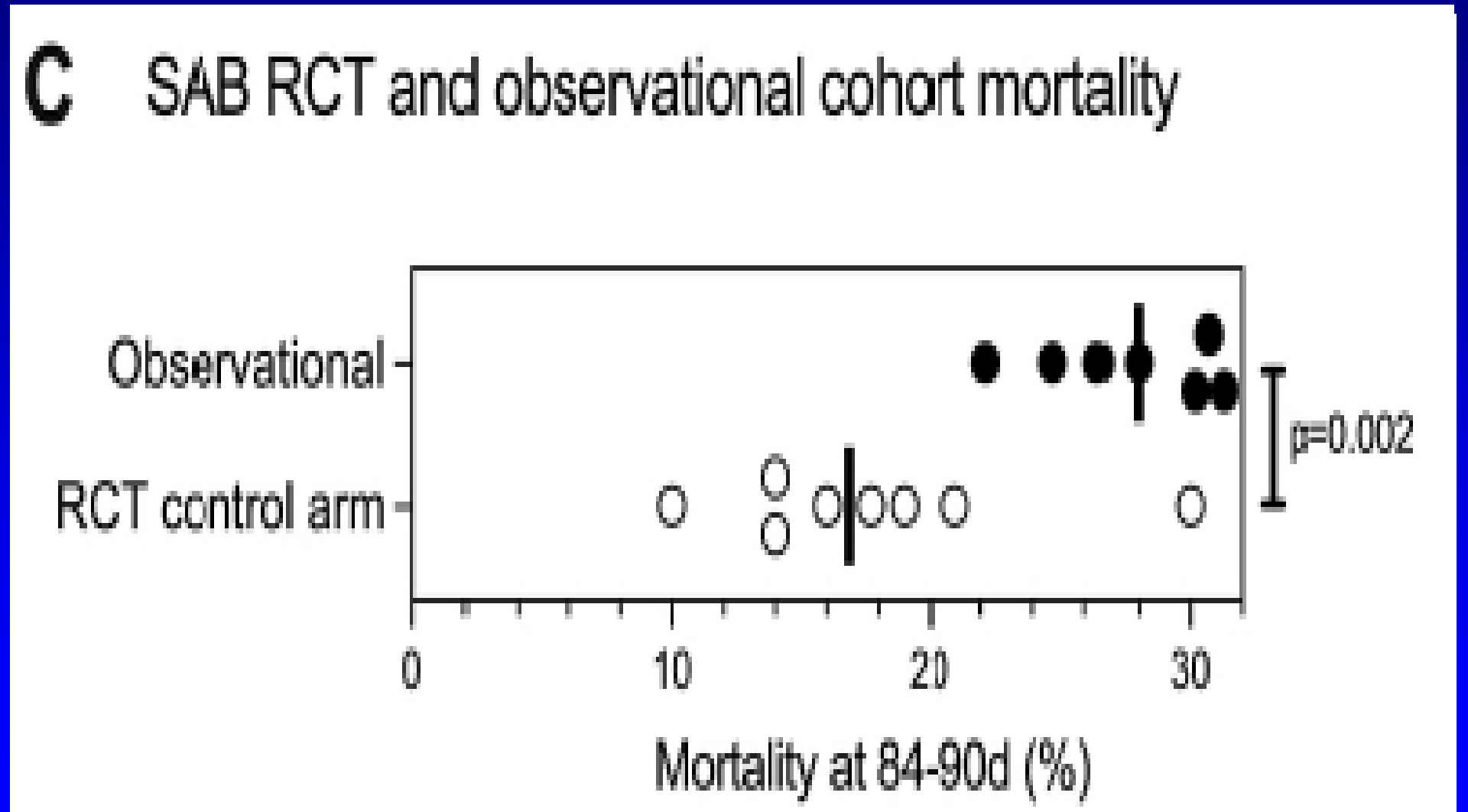
Thomas L. Holland, MD; Christopher Arnold, MD; Vance G. Fowler Jr, MD, MHS

JAMA. 2014;312(13):1330-1341.



Heterogeneity In Staphylococcus aureus Bacteraemia Clinical Trials Complicates Interpretation Of Findings

Heather W. Dolby, Sarah A. Clifford, Ian F. Laurenson, Vance G. Fowler, Jr., Clark D. Russell



Journal of Infectious Diseases 2022 May 27;jiac219. doi: 10.1093/infdis/jiac219. Online ahead of print

Future MICROBIOLOGY

Clinical Trial Protocol

Ceftobiprole versus daptomycin in *Staphylococcus aureus* bacteremia: a novel protocol for a double-blind, Phase III trial

Kamal Hamed*,[1], Marc Engelhardt[1], Mark E Jones[1], Mikael Saulay[1], Thomas L Holland[2], Harald Seifert[3,4] & Vance G Fowler Jr[2]

Bacteriophage for *SAB/IE*

"S. aureus" AND "Bacteriophage"

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Saved Studies

Clear Saved Studies List | Download | Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions
1	☑	Not yet recruiting NEW	Phage Therapy in Prosthetic Joint Infection Due to Staphylococcus Aureus Treated With DAIR.	• Infection of Total Hip Joint Prosthesis • Infection of Total Knee Joint Prosthesis	• Biological: Anti-Staphylococcus aureus Bacteriophages
2	☑	Recruiting	Study Evaluating Safety, Tolerability, and Efficacy of Intravenous AP-SA02 in Subjects With S. Aureus Bacteremia	• Bacteremia • Staphylococcus Aureus • Staphylococcus Aureus Bacteremia • (and 2 more...)	• Biological: AP-SA02 • Other: Placebo

Courtesy Sarah Cantrell, MLIS

nature microbiology

ARTICLES

https://doi.org/10.1038/s41564-019-0634-z

NATURE MICROBIOLOGY | VOL 5 | MARCH 2020 | 465–472 |

There are amendments to this paper

Safety of bacteriophage therapy in severe *Staphylococcus aureus* infection

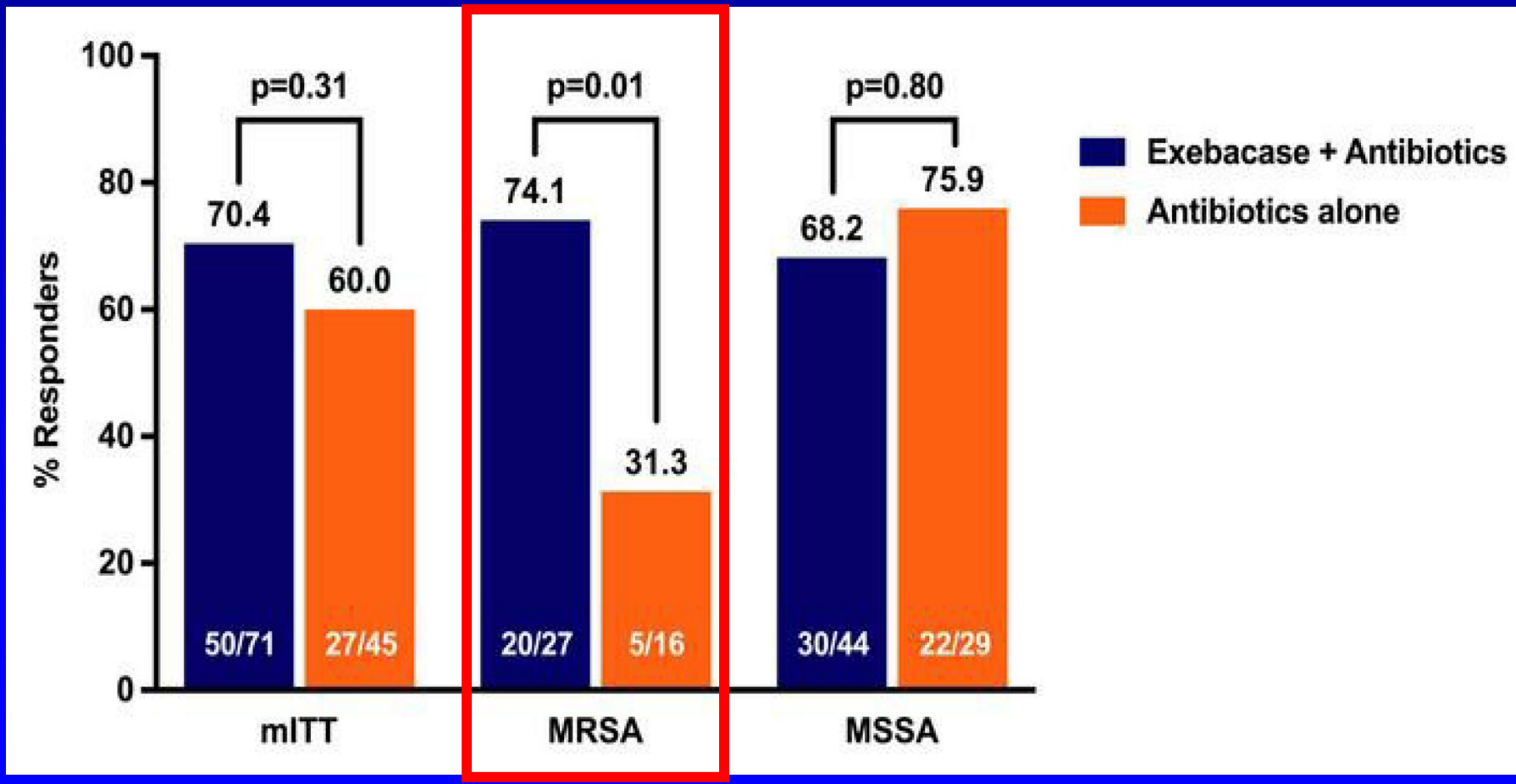
Aleksandra Petrovic Fabijan[1,2,6], Ruby C. Y. Lin[1,2,3,4,6], Josephine Ho[1,2], Susan Maddocks[1,2,3], Nouri L. Ben Zakour[1,3], Jonathan R. Iredell[1,2,3]* and Westmead Bacteriophage Therapy Team[5]

- 13 patients with 2 consecutive days of SAB
- *- 6 Definite IE (4 PVE)*
- Adjunctive Bacteriophage 10^9 q 12h dosing.
- 6/13 (46%) died by D90
- 1 pre-therapy isolate was Resistant to phage
- Well tolerated

Exebacase for patients with *Staphylococcus aureus* bloodstream infection and endocarditis

Vance G. Fowler Jr.,[1,2] Anita F. Das,[3] Joy Lipka-Diamond,[4] Raymond Schuch,[5] Roger Pomerantz,[5] Luis Jáuregui-Peredo,[6] Adam Bressler,[7] David Evans,[8] Gregory J. Moran,[9] Mark E. Rupp,[10] Robert Wise,[11] G. Ralph Corey,[1] Marcus Zervos,[12] Pamela S. Douglas,[1,2] and Cara Cassino[5]

J Clin Invest. 2020. https://doi.org/10.1172/JCI136577.



Other Clinical Trials of Lysins for *S. aureus*

Exebecase Phase 3

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ClinicalTrials.gov

Trial record **1 of 1** for: Exebacase | Phase 3

Previous Study | Return to List | Next Study

Direct Lysis of Staph Aureus Resistant Pathogen Trial of Exebacase (DISRUPT)

Tonabacase Phase 2

NIH U.S. National Library of Medicine

ClinicalTrials.gov

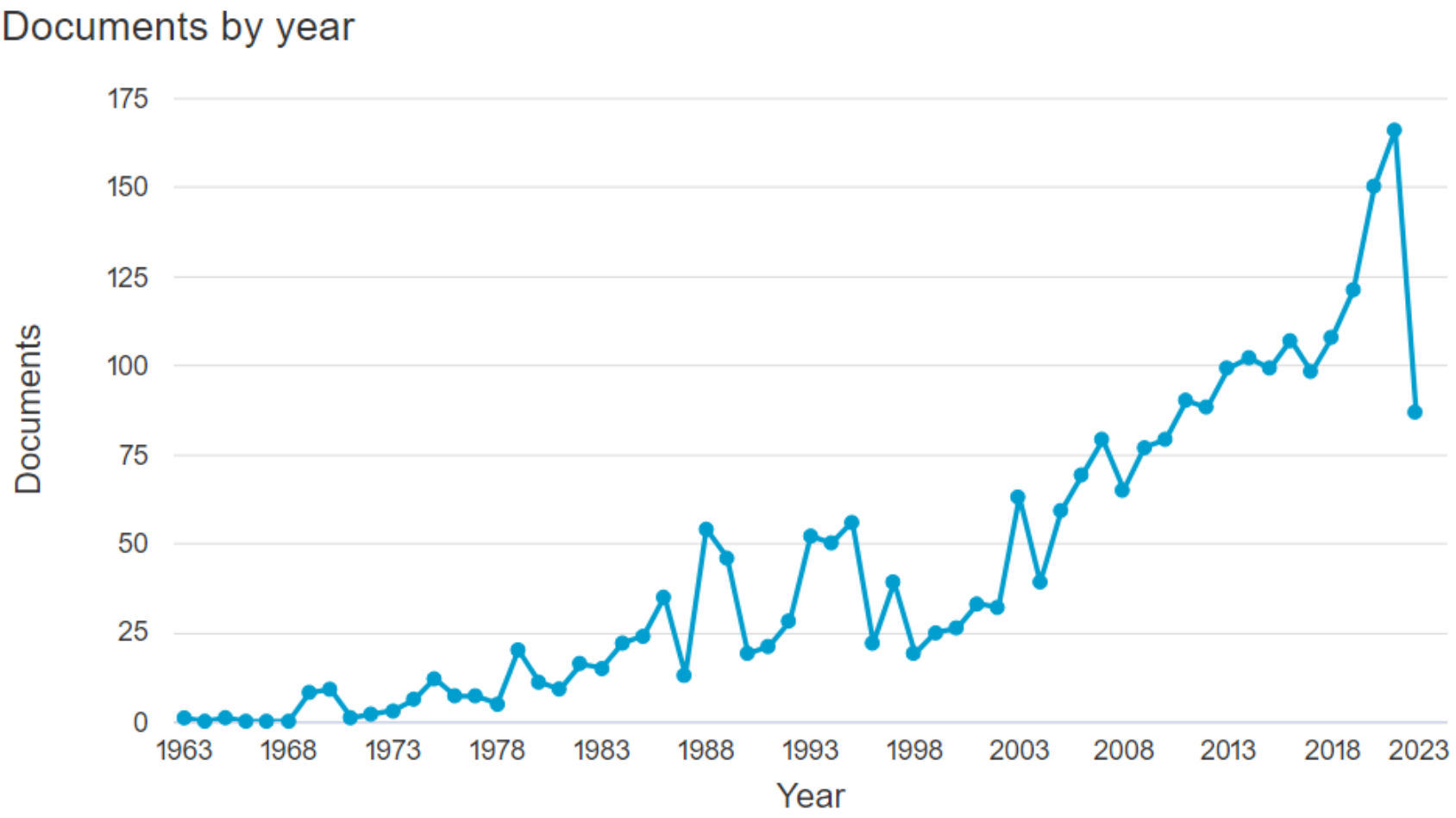
Trial record **5 of 12** for: staphylococcus aureus bacteremia | Staphylococcus Aureus Endocarditis

Previous Study | Return to List | Next Study

ERAdicate S. Aureus in Patients With Bacteremia and Endocarditis (ERASE)

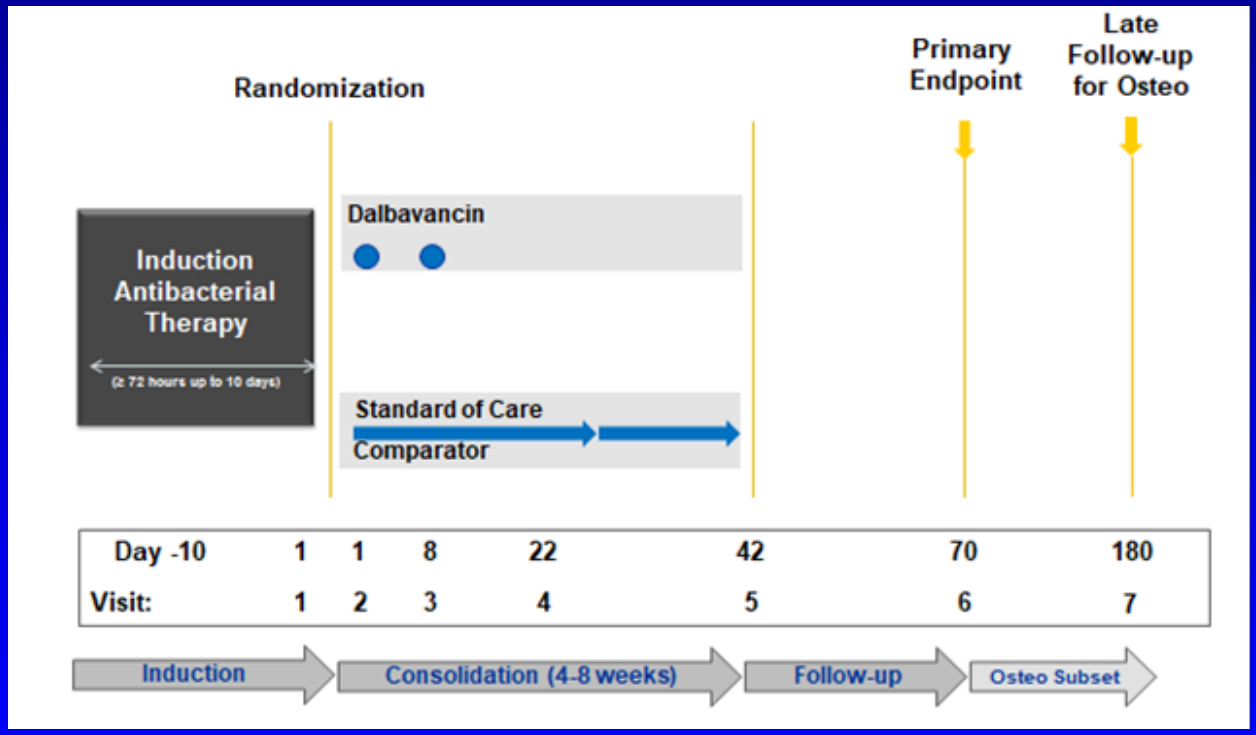
Strategy Trials for *SAB/IE*

(oral antibiotics OR antibiotic duration OR combination therapy).



Courtesy Sarah Cantrell, MLIS

Dalbavancin as an Option for Treatment of *S. aureus* Bacteremia



- Multicenter, randomized, open-label, assessor-blinded study of dalbavancin vs standard of care for completion of treatment in complicated *S. aureus* bacteremia
- **Primary outcome**: superiority by Desirability of Outcome Ranking (DOOR)
- **Secondary outcome**: non-inferiority by clinical response

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ClinicalTrials.gov

RODEO-1

Trial record **44 of 128** for: Endocarditis

Previous Study | Return to List | Next Study

Oral Switch During Treatment of Left-sided Endocarditis Due to Multi-susceptible Staphylococcus

- Nationwide, noninferiority, open-label RCT
- Patients with Left-sided multi-susceptible staphylococcus having received at least 10d IV therapy
- Randomized between D 10 and D 28 after starting IV abx or undergoing surgery to standard IV abx or PO Levofloxacin and Rifampin
- Stratified on valve replacement surgery

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ClinicalTrials.gov

Trial record **3 of 128** for: Endocarditis

Previous Study | Return to List | Next Study

Accelerated Treatment of Endocarditis (POET II)

- Nationwide, noninferiority, open-label RCT
- Patients with Definite IE due to Streptococci, *Enterococcus faecalis*, or *Staphylococcus aureus*
- n~750 (200 patients with IE due to each type of bacteria)
- Abbreviated therapy vs. standard antibiotic duration
- ***Primary endpoint:*** Death, Embolism, recurrent bacteremia, or unplanned surgery

Protocol update for the SABATO trial: a randomized controlled trial to assess early oral switch therapy in low-risk *Staphylococcus aureus* bloodstream infection

Achim J. Kaasch[1,2*], Anna Rommerskirchen[1], Martin Hellmich[3], Gerd Fätkenheuer[4,5], Reinhild Prinz-Langenohl[6], Siegbert Rieg[7], Winfried V. Kern[7], Harald Seifert[5,8], for the SABATO trial group

Kaasch *et al. Trials* (2020) 21:175

- Randomized, parallel-group, observer-blinded, clinical non-inferiority trial
- Low-risk patient
- 5-7d IV + either 7d IV or 7d PO = 14d total duration
- *Status: Presented ECCMID 2022*

Efficacy of seven and fourteen days of antibiotic treatment in uncomplicated *Staphylococcus aureus* bacteremia (SAB7): study protocol for a randomized controlled trial

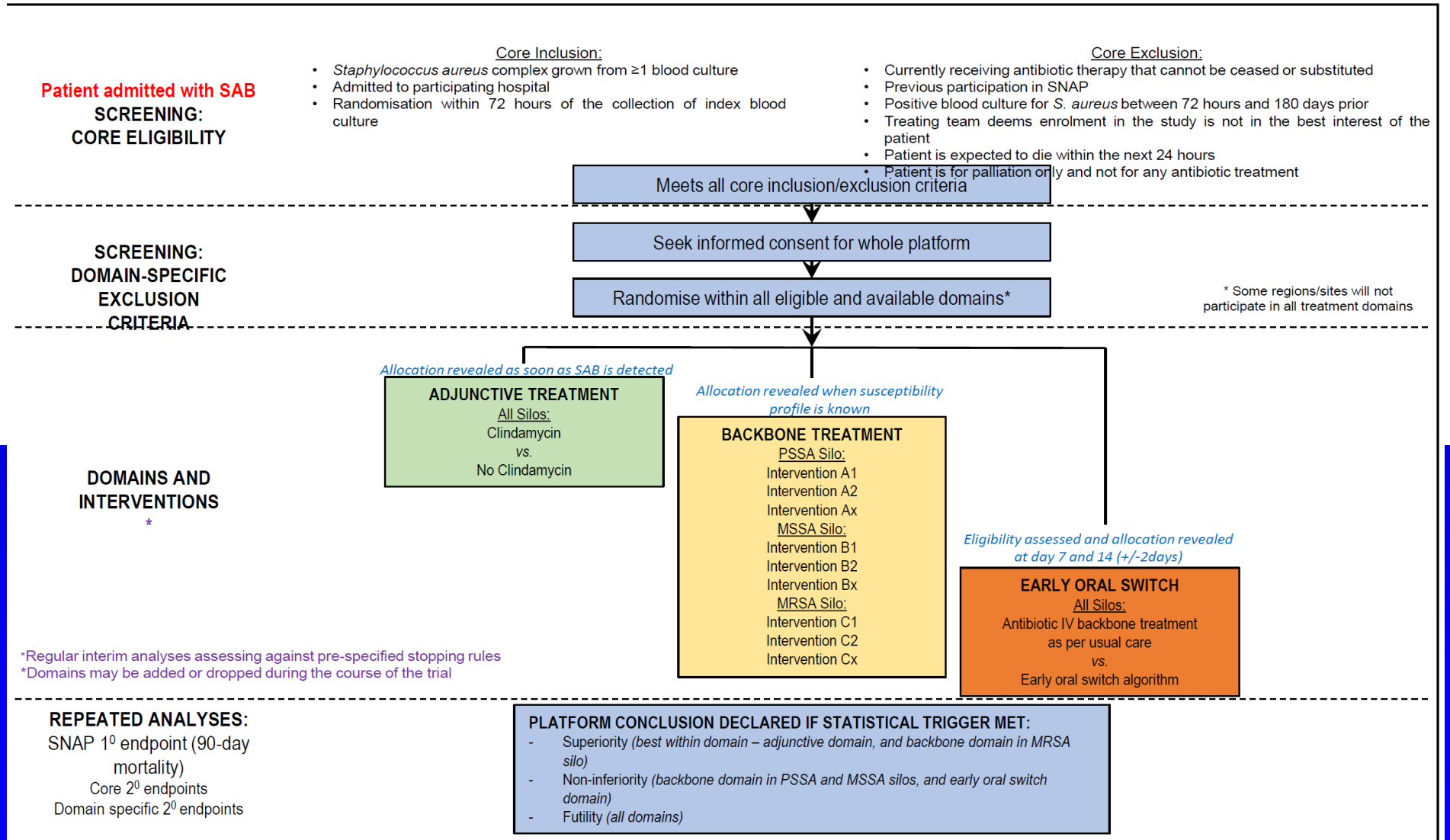
Louise Thorlacius-Ussing[1*], Christian Østergaard Andersen[2], Niels Frimodt-Møller[3], Inge Jenny Dahl Knudsen[2], Jens Lundgren[4] and Thomas Lars Benfield[1]

Inclusion criteria	Exclusion criteria
• Age > 18 years	• Persistence of *S. aureus* bacteremia before randomization (*S. aureus* positive follow-up blood culture obtained within 48–120 h of the first positive blood culture)
• Blood culture positive for *Staphylococcus aureus*	• Polymicrobial infection
• Antibiotic treatment with antimicrobial activity to *S. aureus* administrated within 12 h of the first positive blood culture	• Antibiotic treatment with no antimicrobial activity to *S. aureus* administered more than 12 h after the first positive blood culture
• Temperature < 37,5 °C at randomization	• Endocarditis or other intracardiac infection demonstrated with transthoracic or transesophageal echocardiography
• *S. aureus* negative follow-up blood culture obtained 48–120 h after microbiologically verified SAB	• Previous history of endocarditis
• Patients written consent obtained	• Pacemaker or other intracardiac implant
	• Failure to remove a likely focus of infection, such as central venous catheter, within 72 h of the first positive blood culture
	• Vascular grafts
	• Pneumonia or infection involving bone, joints, or prosthetics
	• Previous bone/joint infection
	• *S. aureus* infection within the last 90 days
	• Pregnancy or breastfeeding
	• Neutropenia (blood neutrophils < 1.0×10^9/l)
	• Untreated cancer
	• Chemotherapy within 90 days.

Staphylococcus aureus Network Adaptive Platform Trial

SNAP

snap@snaptrial.net



Quality of Life: Does Shorter or Oral Therapy Matter for Patients with *S. aureus* bacteremia?

It didn't in OVIVA by European Quality of Life-5

Li et al. N Engl J Med 2019;380:425-36.

	Day 14	Day 42	Day 120	Day 365
Treatment effect for the EQ-5D index PO vs. IV*	-0.003 (-0.052, 0.046), P=0.92	0.005 (-0.057, 0.066), P=0.88	-0.032 (-0.1, 0.035), P=0.35	-0.014 (-0.065, 0.038), P=0.61
N	596	631	554	533
Treatment effect for the EQ-5D VAS PO vs. IV*	0.206 (-3.243, 3.656), P=0.91	2.069 (-1.293, 5.431), P=0.23	-1.64 (-6.082, 2.801), P=0.47	-1.527 (-5.617, 2.562), P=0.46
N	571	610	533	514

Patients' Experiences With *Staphylococcus aureus* and Gram-negative Bacterial Bloodstream Infections: A Qualitative Descriptive Study and Concept Elicitation Phase To Inform Measurement of Patient-reported Quality of Life

Heather A. King,[1,2,3] Sarah B. Doernberg,[4] Julie Miller,[1] Kiran Grover,[1] Megan Oakes,[1] Felicia Ruffin,[5] Sarah Gonzales,[1] Abigail Rader,[6] Michael J. Neuss,[7] Hayden B. Bosworth,[1,2] Zoë Sund,[8] Caitlin Drennan,[9] Jonathan M. Hill-Rorie,[10] Pratik Shah,[11] Laura Winn,[1] Vance G. Fowler Jr,[5,8] and Thomas L. Holland[5,8]; on behalf of the Antibacterial Resistance Leadership Group

Clinical Infectious Diseases 2020 May 23;ciaa611. doi: 10.1093/cid/ciaa611.

SUMMARY:
Future Clinical Trials in SAB & IE

- **Current clinical trials data:**
  inadequate or unavailable

- **New antibiotics:** *Rare*
- **Adjunct agents:** *several potential candidates*
- **Strategy trials:** *Abundant*

- **Clinical trials networks:** *primarily strategy trials*

- **Patient QOL:** *increasingly included*

Future of *S. aureus* Bacteremia & IE

Clinical Trials

Diagnostics

Biofilm

Machine Learning

Prediction Rules for Ruling Out Endocarditis in Patients With *Staphylococcus aureus* Bacteremia

Thomas W. van der Vaart,[1,2] Jan M. Prins,[2] Robin Soetekouw,[3] Gitte van Twillert,[4] Jan Veenstra,[5] Bjorn L. Herpers,[6] Wouter Rozemeijer,[7] Rogier R. Jansen,[8] Marc J. M. Bonten,[1,9] and Jan T. M. van der Meer[2]

Clinical Infectious Diseases® 2022;74(8):1442–9

Table 3. Diagnostic Accuracies of POSITVE, PREDICT, and VIRSTA Scores

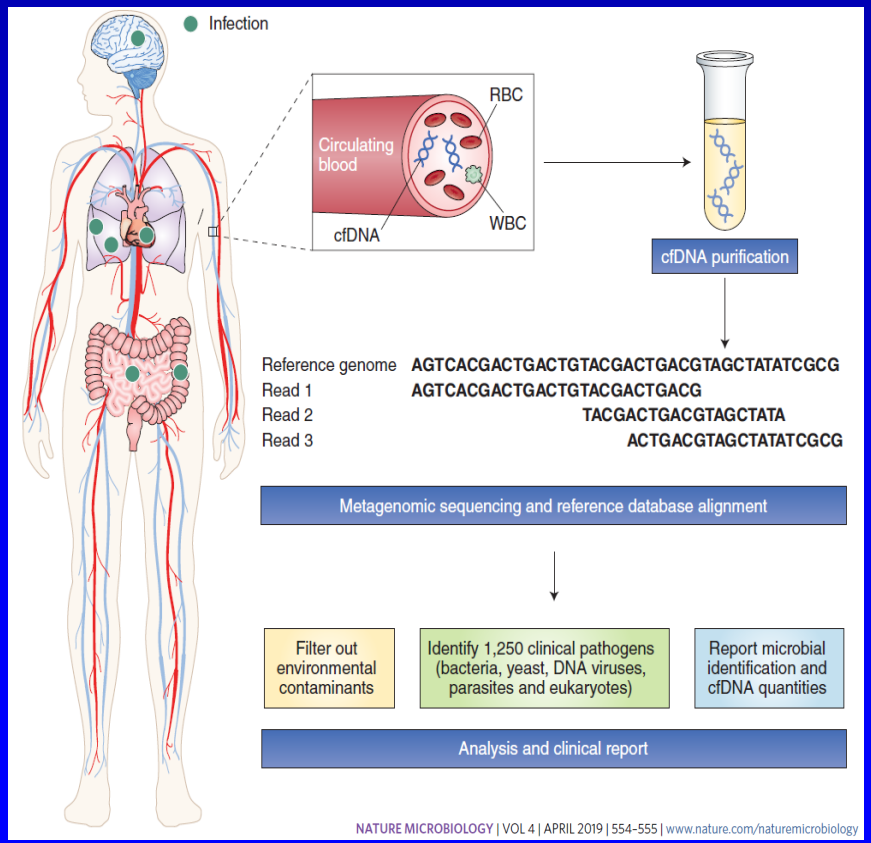
Score	Sensitivity (% + 95% CI)	Specificity (% + 95% CI)	Negative Predictive Value (% + 95% CI)	Positive Predictive Value (% + 95% CI)	AUC
POSITIVE[a]	77.6 (65.8–86.9)	63.1 (57.3–68.6)	92.5 (87.9–95.8)	32.3 (25.1–40.1)	77.8 (71.9–83.7)
PREDICT day 1	22.9 (14.6–33.5)	97.4 (95.3–98.8)	85.0 (81.4–88.2)	66.7 (47.2–82.7)	71.4 (65.2–77.5)
PREDICT day 5	85.1 (75.8–91.8)	56.9 (51.8–61.9)	94.5 (90.7–97.0)	30.5 (24.7–36.8)	79.7 (73.9–85.4)
VIRSTA	98.9 (95.7–100)	35.7 (30.8–40.6)	99.3 (94.9–100)	25.5 (20.7–30.3)	88.9 (85.3–92.5)

Next Generation Diagnostics & Endocarditis

Analytical and clinical validation of a microbial cell-free DNA sequencing test for infectious disease

Timothy A. Blauwkamp[1,3*], Simone Thair[2,3], Michael J. Rosen[1], Lily Blair[1], Martin S. Lindner[1], Igor D. Vilfan[1], Trupti Kawli[1], Fred C. Christians[1], Shivkumar Venkatasubrahmanyam[1], Gregory D. Wall[1], Anita Cheung[1], Zoë N. Rogers[1], Galit Meshulam-Simon[1], Liza Huijse[1], Sanjeev Balakrishnan[1], James V. Quinn[2], Desiree Hollemon[1], David K. Hong[1], Marla Lay Vaughn[1], Mickey Kertesz[1], Sivan Bercovici[1], Judith C. Wilber[1,3] and Samuel Yang[2,3]

NATURE MICROBIOLOGY | VOL 4 | APRIL 2019 | 663–674 | www.nature.com/naturemicrobiology



NATURE MICROBIOLOGY | VOL 4 | APRIL 2019 | 554–555 | www.nature.com/naturemicrobiology

Can cell-free DNA test be used in IE patients to:

1) Diagnose IE

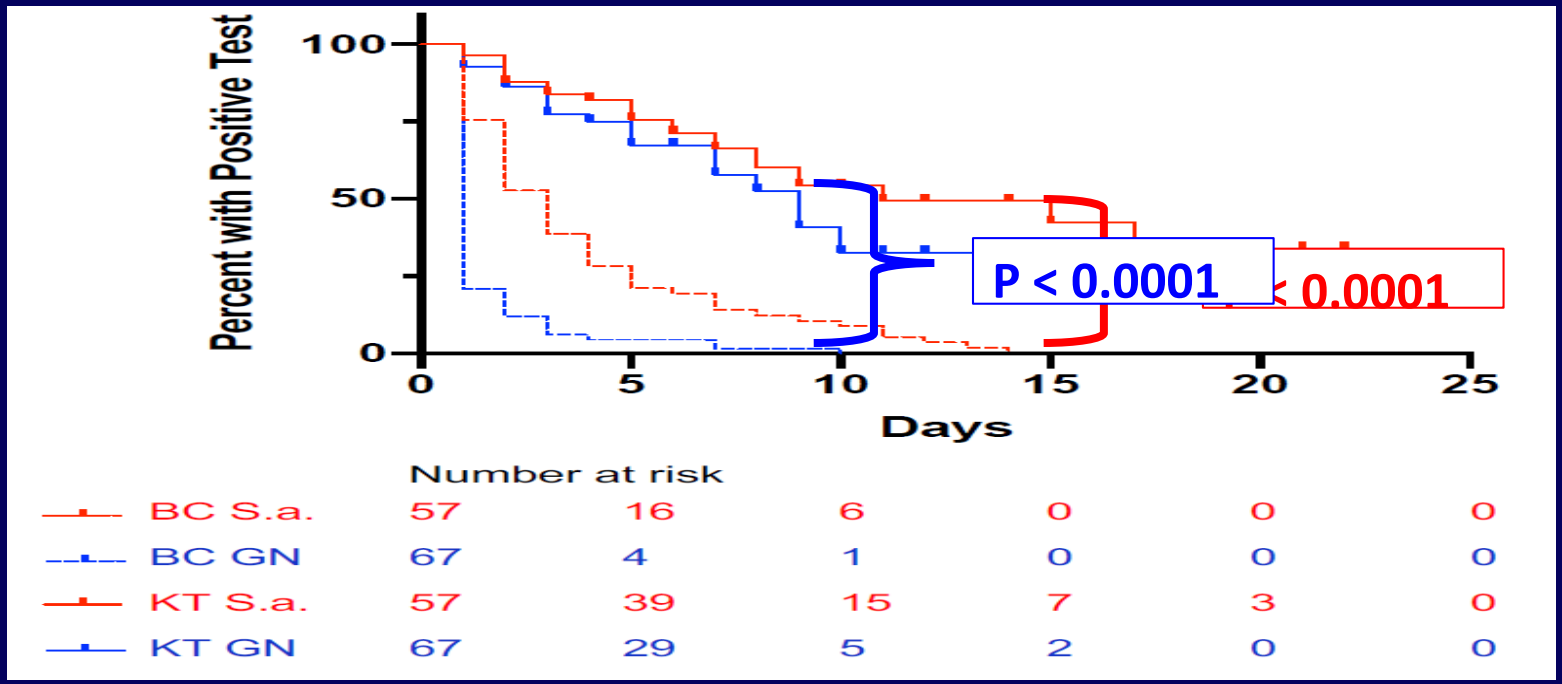
2) Individualize treatment duration

DISCLOSURE: VGF has received Grant funding from Karius & is a Consultant & owns Stock Options with ArcBio

1) Diagnose IE

Microbial Cell-Free DNA Identifies Etiology of Bloodstream Infections, Persists Longer Than Conventional Blood Cultures, and Its Duration of Detection Is Associated With Metastatic Infection in Patients With *Staphylococcus aureus* and Gram-Negative Bacteremia

Emily M. Eichenberger,[1] Christiaan R. de Vries,[2] Felicia Ruffin,[1] Batu Sharma-Kuinkel,[1] Lawrence Park,[1] David Hong,[2] Erick R. Scott,[2] Lily Blair,[2] Nicholas Degner,[2] Desiree H. Hollemon,[2] Timothy A. Blauwkamp,[2] Carine Ho,[2] Hon Seng,[2] Pratik Shah,[3] Lisa Wanda,[4,5] Vance G. Fowler Jr,[1] and Asim A. Ahmed[2]



Clinical Infectious Diseases® 2021;XX(XX):0–0

2) Individualize Treatment Duration

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Microbial Cell-Free DNA Identifies the Causative Pathogen in Infective Endocarditis and Remains Detectable Longer Than Conventional Blood Culture in Patients with Prior Antibiotic Therapy

Emily M. Eichenberger,[1,©] Nicholas Degner,[2] Erick R. Scott,[2] Felicia Ruffin,[1] John Franzone,[1] Batu Sharma-Kuinkel,[1] Pratik Shah,[1] David Hong,[2] Sudeb C. Dalai,[2] Lily Blair,[2] Desiree Hollemon,[2] Eliza Chang,[2] Carine Ho,[2] Lisa Wanda,[1] Christiaan de Vries,[2] Vance G. FowlerJr,[1,©] and Asim A. Ahmed[2]

Valve Surgery ↓ mcf-DNA in IE Patients

Could mcf-DNA individualize therapy?

NEGATIVE: *Stop antibiotics*

Convert to oral antibiotics

POSITIVE: *Search for additional Source*

Clin Infect Dis. 2022 Jun 10;ciac426. doi: 10.1093/cid/ciac426. Online ahead of print.

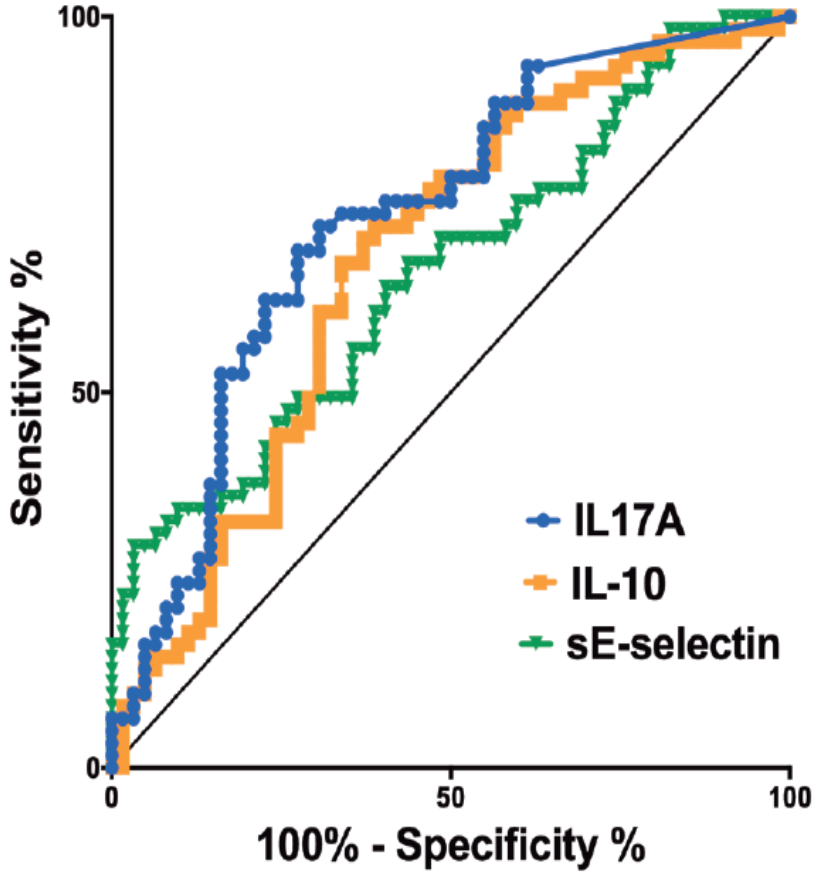
A Prognostic Model of Persistent Bacteremia and Mortality in Complicated *Staphylococcus aureus* Bloodstream Infection

Alessander O. Guimaraes,[1,a] Yi Cao,[1,a] Kyu Hong,[1] Oleg Mayba,[1] Melicent C. Peck,[1] Johnny Gutierrez,[1] Felicia Ruffin,[2] Montserrat Carrasco-Triguero,[1] Jason B. Dinoso,[1] Angelo Clemenzi-Allen,[3] Catherine A. Koss,[3] Stacey A. Maskarinec,[2] Henry F. Chambers,[3] Vance G. Fowler Jr,[2] Amos Baruch,[1] and Carrie M. Rosenberger[1,©]

A

	ROC AUC	P Value
IL–17A	0.731	<0.001
IL–10	0.675	0.001
sE–selectin	0.658	0.002
IL–1RN	0.624	0.018
sIL2RA	0.622	0.02
IL–27	0.617	0.026
IL–6	0.612	0.032
LCN2	0.612	0.033

B



Clinical Infectious Diseases® 2019;68(9):1502–11

Human DNA methylation signatures differentiate persistent from resolving MRSA bacteremia

Yu-Ling Chang[a], Maura Rossetti[a], David W. Gjertson[a,b], Liudmilla Rubbi[c], Michael Thompson[c], Dennis J. Montoya[d], Marco Morselli[c], Felicia Ruffin[e], Alexander Hoffmann[f], Matteo Pellegrini[c], Vance G. Fowler Jr[e,1], Michael R. Yeaman[g,h,i,j,1], Elaine F. Reed[a,1,2], and with the MRSA Systems Immunology Group[3]

- Distinct DNA methylome signature in patients with Persistent and Resolving MRSA bacteremia
- ***Persistent SAB:*** ↓methylation in CCAAT enhancer binding protein B & signal transducer/activator of transcription (STAT1)
- ***Resolving SAB:*** ↓methylation glucocorticoid receptor & histone acetyltransferase p300 site
- Mean AUC 0.85; validated by targeted bisulfite sequencing

PNAS 2021 Vol. 118 No. 10 e2000663118

SUMMARY:
Future Diagnostics in SAB & IE

- **Today:** *TEE with VIRSTA* $\geq$ *3*

- **Eventually:** *Individualize diagnosis & treatment*
  mcf-DNA (?)
  Serological Biomarkers (?)
  Host epigenetic signatures (?)

Biofilm

npj | Biofilms and Microbiomes

www.nature.com/npjbiofilms

ARTICLE OPEN

Check for updates

Alternating magnetic fields and antibiotics eradicate biofilm on metal in a synergistic fashi

Qi Wang[1], Jonathan Vachon[2], Bibin Prasad[1], Christi[3], Norman Chopra[1,4] and David E. Greenberg[3,5]✉

Medicine (2021) 100:44

Observational Stud

Evaluation treatment titanium pl

Jiantong Wei, MD[a,b], Xue
Qinliuye Su, BS[a], Yongpi

Abdelraheem et al.
Ann Clin Microbiol Antimicrob (2021) 20:
https://doi.org/10.1186/s12941-021-00459-

RESEARCH

Effect of ZnO nanop vancomycin, linezol formation in *Staphy*

Wedad M. Abdelraheem, Rasha M. M. Khairy*

Archives of Microbiology (2021) 203:498
https://doi.org/10.1007/s00203-021-02485-2

ORIGINAL PAPER

Check for updates

1,4-Naphthoquinone disinteg es the pre-existing biofilm of *Staphylococcus aureus* by ac umulating reactive oxygen species

Payel Paul[1] · Sharmistha Das[1] · Sudipta Chatterjee[1] · Aditya Shukla[2] · Poulomi Chakraborty[1] · Sarita Sarkar[3] · Debasish Maiti[4] · Amlan Das[5] · Prosun Tribedi[1]

Brazilian Journal of Microbiology (2021) 52:6
https://doi.org/10.1007/s42770-021-00455

SBM Brasileira de Microbiologia

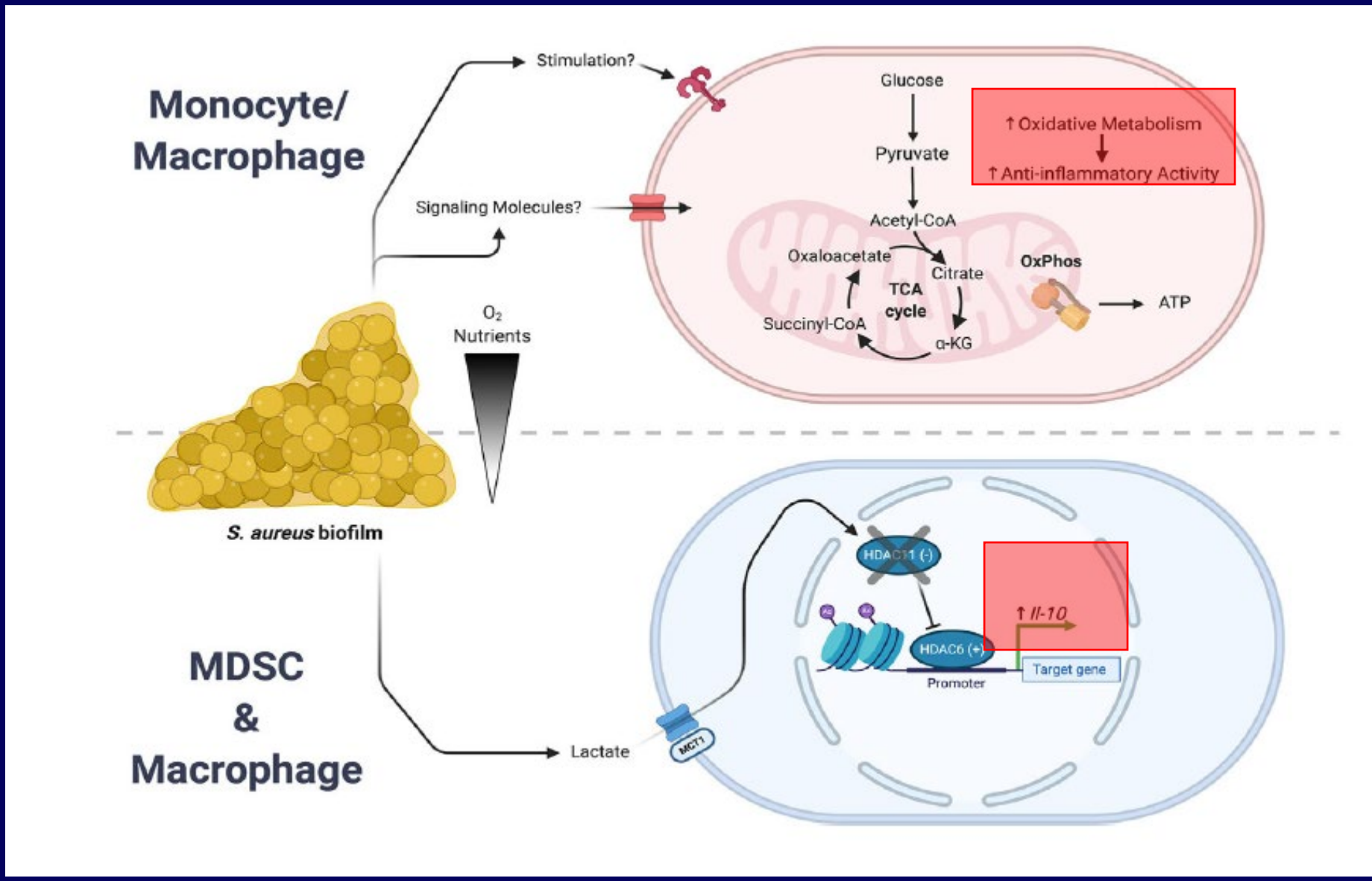
CLINICAL MICROBIOLOGY - RE

Check for updates

Antimicrobial effect of gold nanoparticles in the formation of the *Staphylococcus aureus* biofilm on a polyethylene surface

Lorena Dafnee Villa-García[1] · Raúl Márquez-Preciado[1] · Marine Ortiz-Magdaleno[2] · Olga Araceli Patrón-Soberano[3] · Marco Antonio Álvarez-Pérez[4] · Amaury Pozos-Guillén[2] · Luis Octavio Sánchez-Vargas[5]

S. aureus Biofilm Metabolites ↓ Inflammation



Yamada *PLOS Pathogen* 2020; 16(3): e1008354.

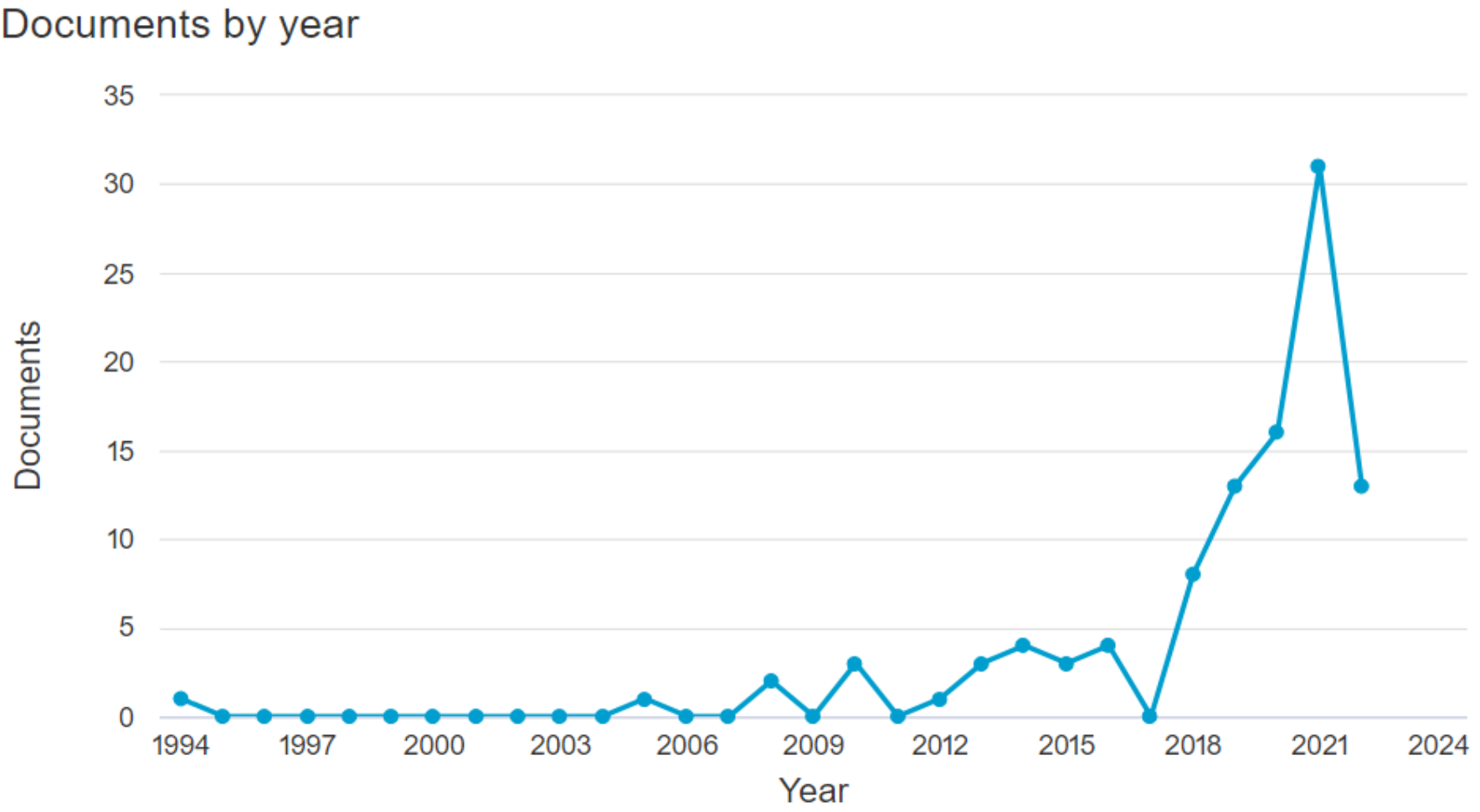
SUMMARY:
Biofilm, *S. aureus*, and the Future

The problem of biofilm-based infection will not be overcome until we understand how the bacteria avoids local host immune response

Machine Learning

Machine Learning for *SAB/IE*

"S. aureus" AND "Artificial Intelligence" OR "Machine Learning"



Courtesy Sarah Cantrell, MLIS

Direct antimicrobial resistance prediction from clinical MALDI-TOF mass spectra using machine learning

NATURE MEDICINE | VOL 28 | JANUARY 2022 | 164-174 | www.nature.com/naturemedicine

Caroline Weis[1,2] ✉, Aline Cuénod[3,4], Bastian Rieck[1,2], Olivier Dubuis[5], Susanne Graf[6], Claudia Lang[5], Michael Oberle[7], Maximilian Brackmann[8], Kirstine K. Søgaard[3,4], Michael Osthoff[9,10], Karsten Borgwardt[1,2,11] ✉ and Adrian Egli[3,4,11] ✉

- Machine learning to predict AMR from MALDI-TOF Mass Spectra profiles of clinical isolates
- Trained & Validated on >300,000 mass spectra with > 750,000 AMR Phenotypes
- Receiver Operating Curves: *S. aureus*: 0.80

  Escherichia coli & Klebsiella pneumoniae: 0.74
- *MALDI-TOF Mass Spectra based Machine learning may thus be an important new tool for treatment optimization*
- ***My take: Necessary but Insufficient for IE***

Original Investigation | Critical Care Medicine

Development and Validation of a Machine Learning Model to Estimate Bacterial Sepsis Among Immunocompromised Recipients of Stem Cell Transplant

Margaret L. Lind, MPH; Stephen J. Mooney, PhD; Marco Carone, PhD; Benjamin M. Althouse, PhD; Catherine Liu, MD; Laura E. Evans, MD; Kevin Patel, MD; Phuong T. Vo, MD; Steven A. Pergam, MD, MPH; Amanda I. Phipps, PhD, MPH

JAMA Network Open. 2021;4(4):e214514. doi:10.1001/jamanetworkopen.2021.4514

- Create a full risk factor & clinic factor-specific automated sepsis decision tool using electronic medical record
- 1943 Stem cell transplant patients divided 70:30 into modeling & validation
- ***Primary outcome:*** High sepsis risk bacteremia (Gram-negative, *S. aureus*, Streptococcus)
- ***Result: Full decision support tool*** had Highest AUC (0.85: 0.81-0.89) for high sepsis-risk Bacteremia: overall, inpatients, outpatients, and 10-day and 28-day mortality
- Full decision tool had superior prognostic accuracy for high-risk sepsis bacteremia and mortality

SUMMARY:
Future of Machine Learning in SAB

- **Today:** *Unproven promise*
- **Eventually:** *Differentiate high risk SAB vs. low-risk SAB ?*

Where are We Going? S. aureus Bacteremia/ IE

Epidemiology & Microbiology:

Healthcare & IDU, ↑↑ Devices, New Clones

Clinical Trials:

Test existing antibiotics >> Approve new antibiotics

Diagnostics:

New tools to differentiate Uncomplicated and Complicated SAB

Biofilm:

Better understanding of host immunology

Machine Learning: *Promising but unproven*