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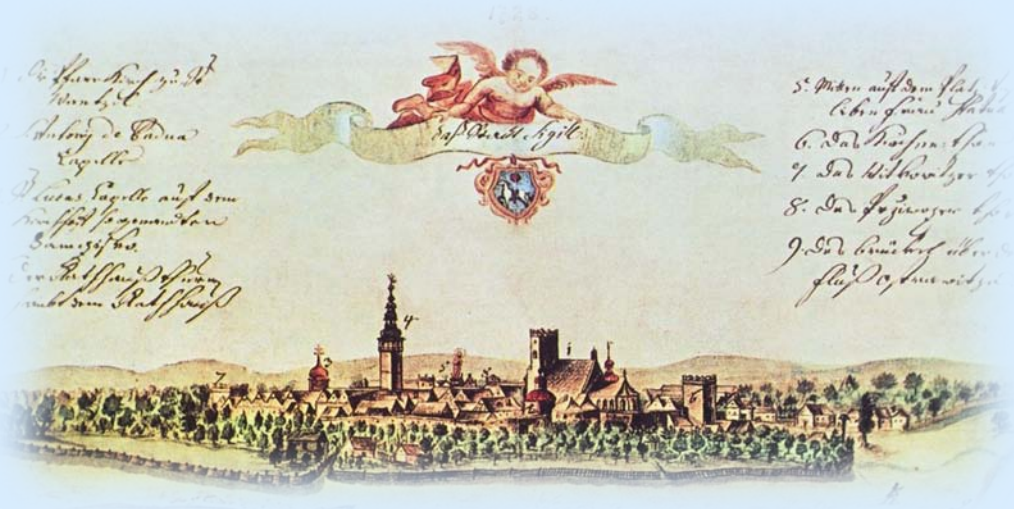
Center for Clinical Studies

18th COLOURS of Sepsis
Join us in Ostrava



Epidemiology and management of Staph. aureus bacteremia

Bundesministerium für Bildung und Forschung

Bundesministerium für Gesundheit

Freistaat Thüringen Ministerium für Arbeit, Soziales, Gesundheit, Frauen und Familie

Ostrava, 27.01.2016

Univ.- Prof. Dr. med. Frank M. Brunkhorst
Jena University Hospital

Center for Sepsis Control & Care

Agenda

- **Sepsis epidemiology in Germany**
- **The goldstandard: blood cultures**
- **Clinical decision making: expert care**

Agenda

- **Sepsis epidemiology in Germany**
- The goldstandard: blood cultures
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Sepsis epidemiology 2011

	Total		R65.0! (Sepsis)		R65.1! (severe Sepsis)		R57.2! (sepic Shock)		*p*-value
	n = 175,051		n = 87,150		n = 69,016		n = 18,885		
Number of cases									
Female, n (%)	76,495	(43.7)	39,434	(45.2)	29,490	(42.7)*	7,571	(40.1)*	< 0.001
Age, mean (SD)	67.5	(19.7)	65.8	(22.1)	69.4	(17.1)*	68.4	(15.1)*	< 0.001
ICU admission, n (%)	66,102	(37.8)	17,073	(19.6)	35,003	(50.7)*	14,026	(74.3)*	< 0.001
Mortality, n (%)	50,098	(28.6)	9,160	(10.5)	29,508	(42.8)*	11,430	(60.5)*	< 0.001

* pairwise comparison with R65.0! (Bonferroni correction for multiple comparisons)

Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

Sepsis epidemiology 2011

Preexisting conditions	Total n = 175,051		R65.0 n = 87,150		R65.1 n = 69,016		R57.2 n = 18,885		*p*-value
Diabetes	56.184	(32.1)	26.338	(30.2)	23.572	(34.2)**	6.274	(33.2)**	< 0.001
Cardiovascular	70.229	(40.1)	27.681	(31.8)	33.328	(48.3)**	9.220	(48.8)**	< 0.001
Cerebrovascular	24.210	(13.8)	10.893	(12.5)	10.650	(15.4)**	2.667	(14.1)**	< 0.001
Renal dysfunction	49.186	(28.1)	21.771	(25)	22.198	(32.2)**	5.217	(27.6)**	< 0.001
COPD	20.442	(11.7)	8.464	(9.7)	9.114	(13.2)**	2.864	(15.2)**	< 0.001
Liver cirrhosis	15.296	(8.7)	3.571	(4.1)	8.013	(11.6)**	3.712	(19.7)**	< 0.001
Hematological	23.031	(13.2)	6.715	(7.7)	11.004	(15.9)**	5.312	(28.1)**	< 0.001

Rresults are given as number (%) or mean (SD), *p* between groups.
*$p < 0.05$, **$p < 0.001$ pairwise comparison with R65.0 (Bonferroni correction for multiple comparisons)

R65.0 = sepsis
R65.1 = severe sepsis
R57.2 = septic shock

Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

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Sepsis epidemiology 2011

Site of infections	Total n = 175,051		R65.0 n = 87,150		R65.1 n = 69,016		R57.2 n = 18,885		*p*-value
Respiratory	68.814	(79)	24.192	(27.8)	33.258	(48.2)**	11.364	(60.2)**	< 0.001
Genitourinary	24.808	(28.5)	12.966	(14.9)	10.031	(14.5)	1.811	(9.6)**	< 0.001
Wound / Soft-tissue	34.094	(39.1)	15.201	(17.4)	14.048	(20.4)**	4.845	(25.7)**	< 0.001
Central nervous system	2.876	(3.3)	1.260	(1.4)	1.296	(1.9)**	320	(1.7)*	< 0.001
Abdominal	27.274	(31.3)	9.912	(11.4)	12.469	(18.1)**	4.893	(25.9)**	< 0.001
Other/Heart	3.409	(3.9)	982	(1.1)	1.856	(2.7)**	571	(3)**	< 0.001

Results are given as number (%) or mean (SD), *p* between groups.

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Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

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Sepsis epidemiology 2011

Pathogens	Total		R65.0		R65.1		R57.2		*p-value*
	n = 80,890		n = 41,898		n = 26,647		n = 12,345		
Staphylococcus aureus	21.700	(26.8)	9.427	(22.5)	7.212	(27.1)**	5.061	(41)**	< 0.001
Streptococcus	15.135	(18.7)	8.106	(19.3)	5.520	(20.7)**	1.509	(12.2)**	< 0.001
E.coli	36.194	(44.7)	21.191	(50.6)	10.393	(39)**	4.610	(37.3)**	< 0.001
Pseudomonas	3.710	(4.6)	1.743	(4.2)	1.517	(5.7)**	450	(3.6)*	< 0.001
Candida	3.593	(4.4)	1.197	(2.9)	1.756	(6.6)**	640	(5.2)**	< 0.001
Haemophilus	308	(0.4)	135	(0.3)	129	(0.5)*	44	(0.4)	0,003
Meningococcus	250	(0.3)	99	(0.2)	120	(0.5)**	31	(0.3)	< 0.001

Results are given as number (%) or mean (SD), *p* between groups.

*$p < 0.05$, **$p < 0.001$ pairwise comparison with R65.0 (Bonferroni correction for multiple comparisons)

R65.0 = sepsis
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Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

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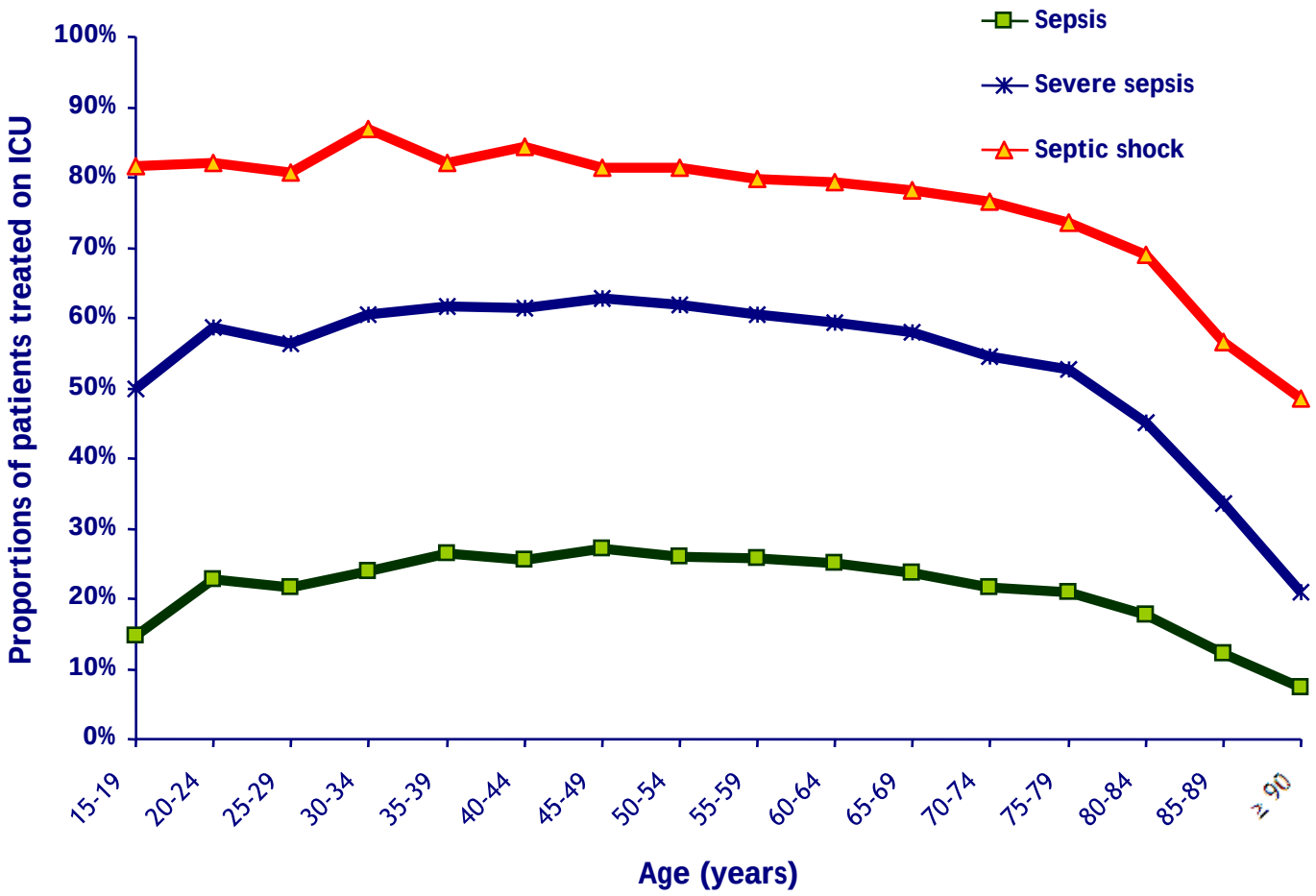
Sepsis epidemiology 2011

Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

Sepsis epidemiology 2011

Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

Sepsis epidemiology 2011



Heublein S, Hartmann M, Hagel S, Brunkhorst FM: Infection 2013

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Sepsis Registry Jena

	2011 N=388 *	2012 N=389 *
Mortality (no., %, 95% CI)		
ICU	130 (33.51%) [28.99;38.34]	118 (30.33%) [25.98;35.08]
Hospital	182 (46.91%) [42.00;51.88]	171 (43.96%) [39.11;48.93]
6-months after discharge	227 (60.70%) [55.66;65.51]	233 (62.30%) [57.29;67.06]
12-months after discharge	246 (67.40%) [62.43;72.00]	251 (65.2%)
24-months after discharge	265 (71.8%)	-

* ICU patients only (120-beds)

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International comparison

Study	Design / data collection	[n]	Hospital M…	ICU stay	Hospital stay (d)
Kaukonen et al. (2014) *Australien / Neuseeland, 2011*	Retrospektive, incidence, administrative data	1…		(1,6-6,9)	13,5 (7,0-25,9)
Levy et al. (2012) *USA, 2005-2010*	Prospektive, registry, not representative	18,766	**28,3%**	4,2 (2,2-8,9)	10,5 (5,8-18,9)
Europe 2005-2010		6,609	**41,1%**	7,8 (3,4-17,2)	22,8 (11,1-43,3)
Heublein et al. (2013) *Deutschland, 2011*	Retrospektive, incidence study, administrative data	89,907	**46,5%**	-	-
Engel et al. (2004) *Deutschland, 2003*	Prospektive, one-day prevalence, representative	415	**55,2%**	12,3 (6-16)	24 (13-38)
Jena Sepsisregistry *Deutschland (Jena), 2011*	Prospektiv, monocentric, incidence study, registry	388	46,9%	10 (4-23)	27 (16-43,2)

Doubling!

In Hospital mortality AND stay

Brunkhorst FM et al. IntensivNews 2014

Agenda

- Sepsis epidemiology in Germany
- **The goldstandard: blood cultures**
- Clinical decision making: expert care

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Bloodstream Infections & Blood Culture Diagnostics

Bloodstream infections (BSIs) are a leading cause of death worldwide

Limitations of existing BSI surveillance studies:

- not representative of the population,
- no hospital-, patient-, and laboratory-based denominator data,
- not directly used to improve health care,
- *"The more you take, the more you find"*: Germany among weakest BC, testing performers in Europe (annually ECDC reports).

Gaynes R (1995) Surveillance of antibiotic resistance: learning to live with bias. Infect Control Hosp Epidemiol 16: 623-6
Sogaard M et al (2013) Monitoring the epidemiology of bloodstream infections: aims, methods and importance. Expert Rev Anti Infect Ther 11: 1281-90
Laupland KB et al (2009) Rationale for and protocol of a multi-national population-based bacteremia surveillance collaborative. BMC Res Notes 2: 146
Schmitz RPH et al (2013) Quality of blood culture testing – a survey in intensive care units and microbiological laboratories across four European countries. Crit Care 17: R248

PLOS | ONE

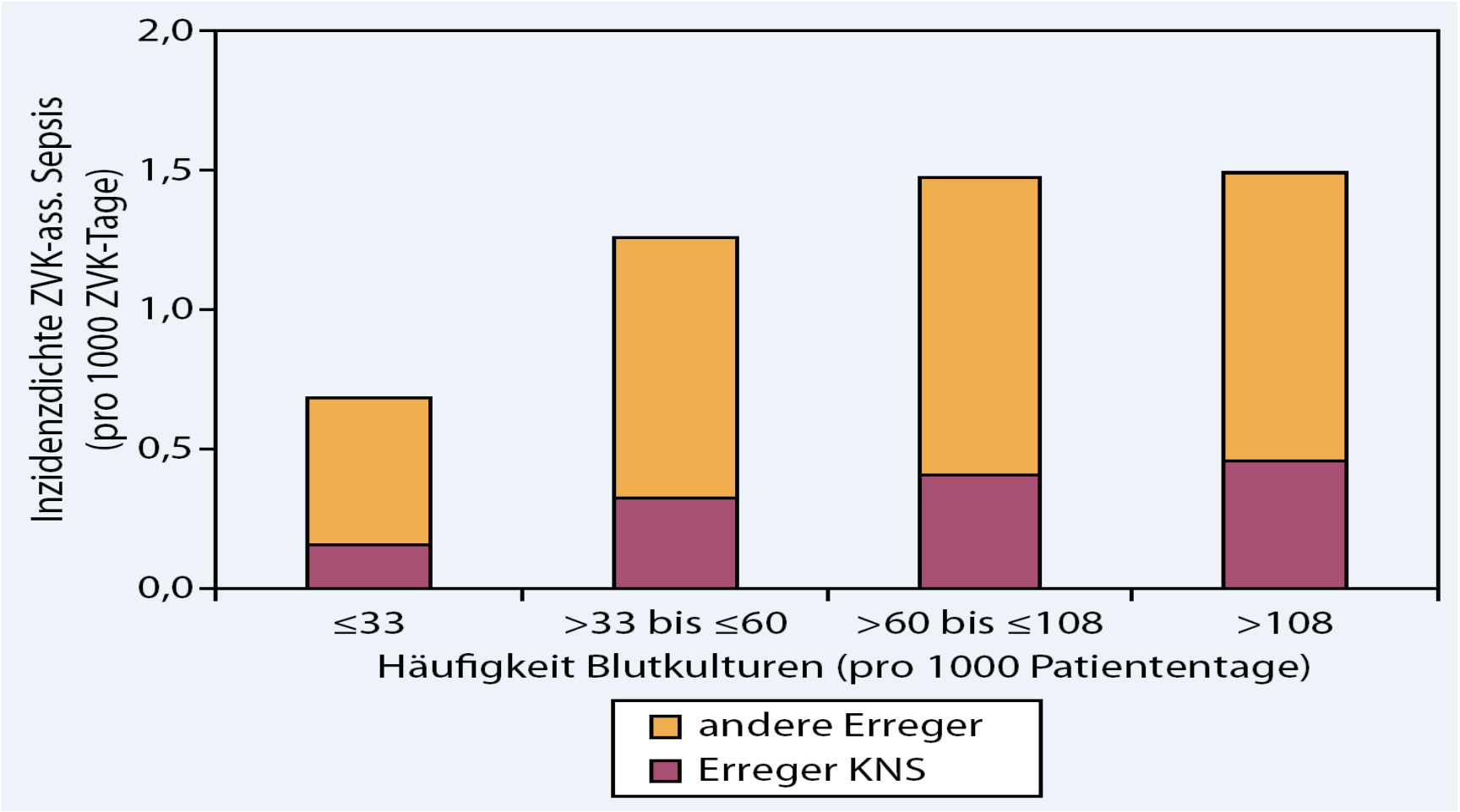
RESEARCH ARTICLE

Low Completeness of Bacteraemia Registration in the Danish National Patient Registry

- **Gold standard:** bacteraemia patients in three defined areas of Denmark (~2.3 million inhabitants) from 2000 - 2011 by use of blood culture data retrieved from electronic microbiology databases
- **Comparator:** hospital discharge diagnoses (ICD 10)
- 58,139 bacteraemic episodes in 48,450 patients
- Only 37,740 episodes (64.9%) were covered by hospital discharge diagnoses
- Administrative data should be used cautiously to identify patients with bacteraemia

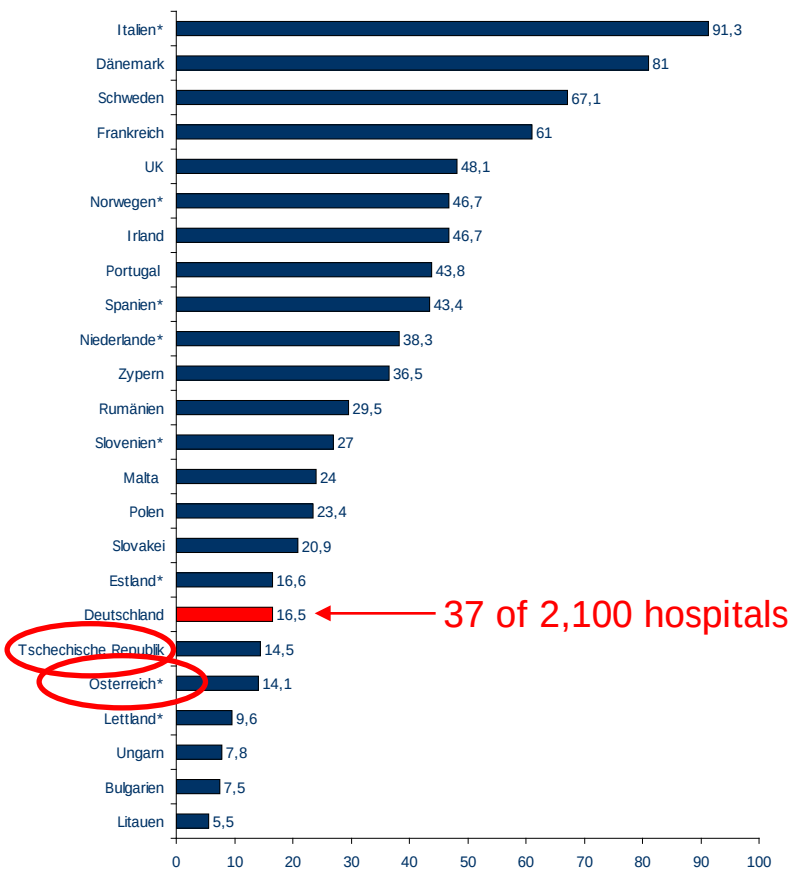
PLoS ONE 10(6):2015; e0131682. doi:10.1371/journal.pone.0131682

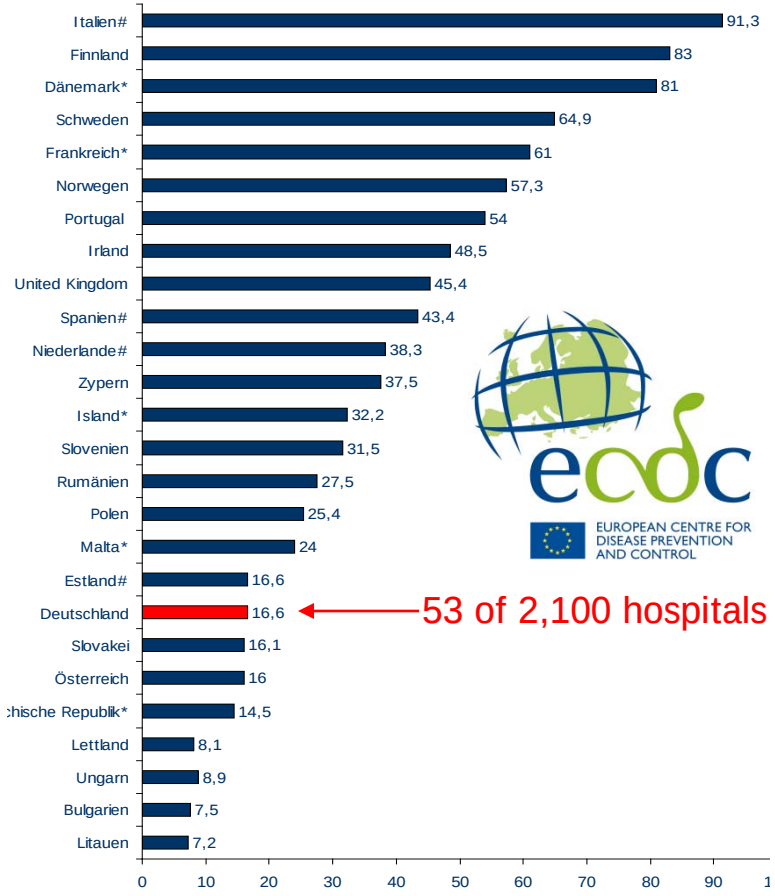
Blood culture diagnostics on German ICUs



Gastmeier P et al. Anaesthesist 2011, 60:902-907

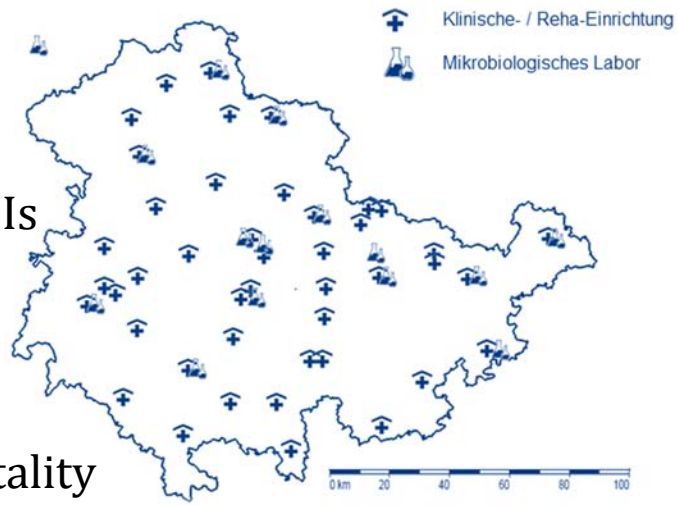
Blood culture pairs per 1000 patient days (EARS)





ÊCDC/EARS Report 2010 and 2011: Antimicrobial resistance surveillance in Europe, http://www.ecdc.europa.eu).

Population basis?



- Best approach for defining the burden of BSIs
- Defined population of risk:

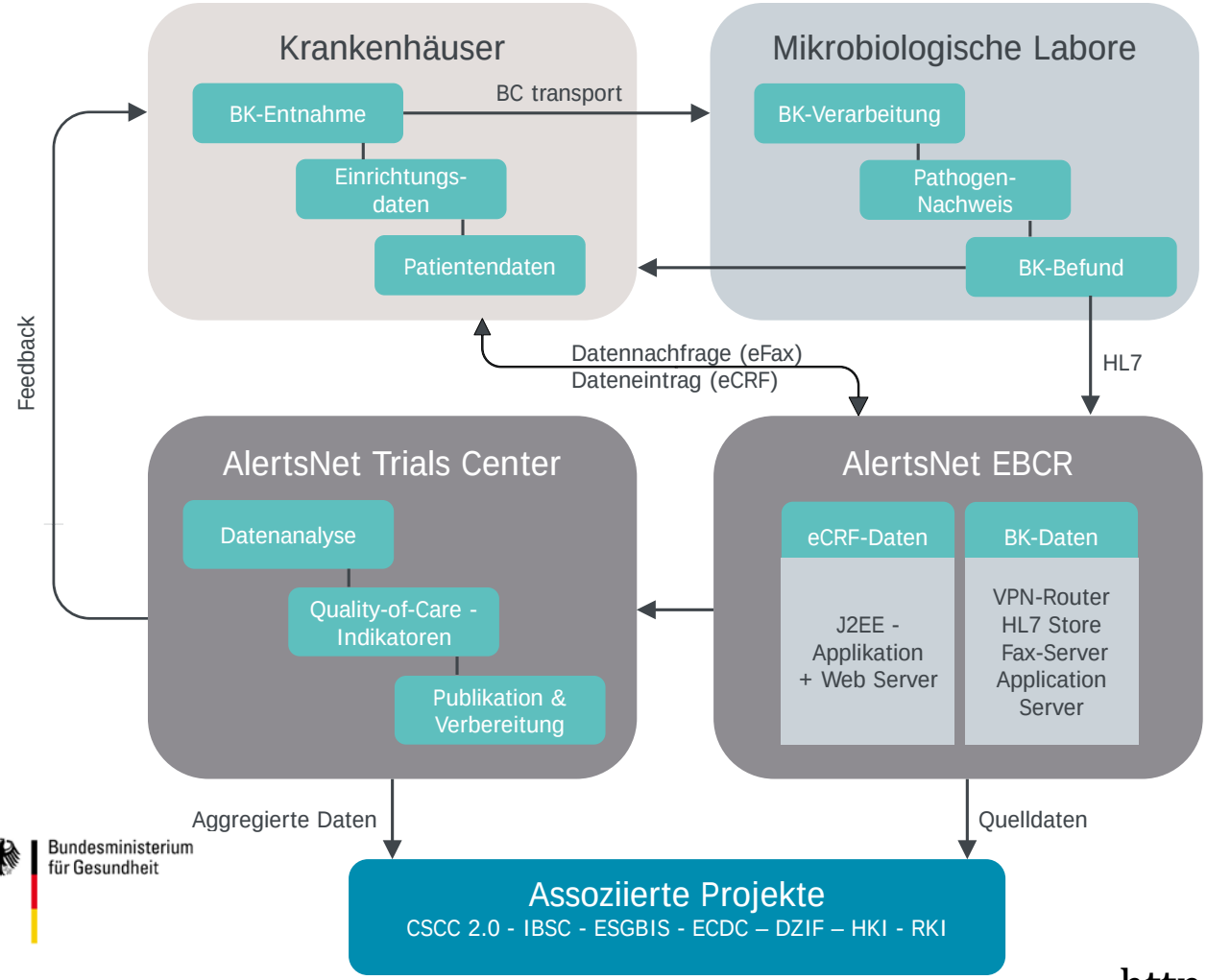
  - minimized selection bias

  - adjusted calculation of incidence and mortality
- Evaluation of risk factors for infections
- Monitoring temporal trends in occurrence and resistance of pathogens
- Monitoring usage and trends in the application of anti-infective treatment

Objective: attendance of all Thuringian clinical facilities with BC diagnostics

Laupland KB, Gregson DB, Flemons WW, et al. Burden of community-onset bloodstream infection: a population-based assessment. Epidemiology and infection 2007;135(6):1037-42
Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive care medicine 2007;33(4):606-18
Laupland KB. Defining the epidemiology of bloodstream infections: the 'gold standard' of population-based assessment. Epidemiology and infection 2013;141(10):2149-57

Population-based Surveillance of BSI´s



AlertsNet Thüringen

Sample size

- Eligible: ~316,000 BC sets/year
- Assigned: ~25,300 positive BC sets/yr
- Analyzed: ~20,200 clinically relevant positive BC sets in ~5,000 patients/yr

Participating centers & study duration

- 34 hospitals (20,403 hospital beds), 19 microbiological labs
- 2013-2020

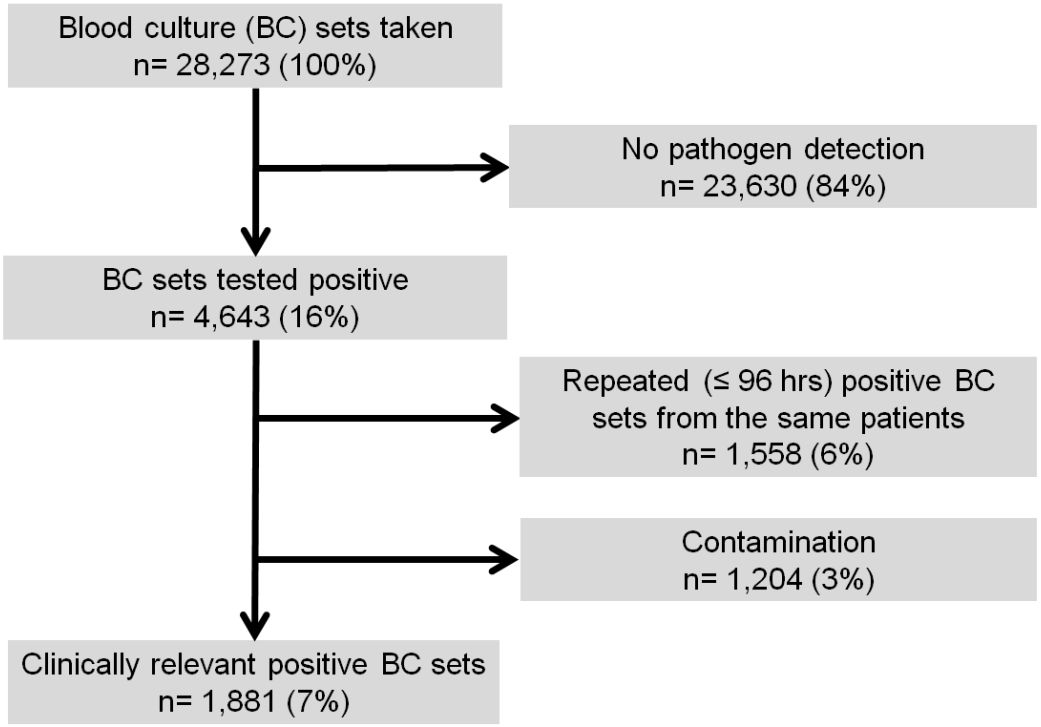
http://www.alertsnet.de/

Bundesministerium für Gesundheit

Results from the first 12-months report

- BC positivity and contamination -

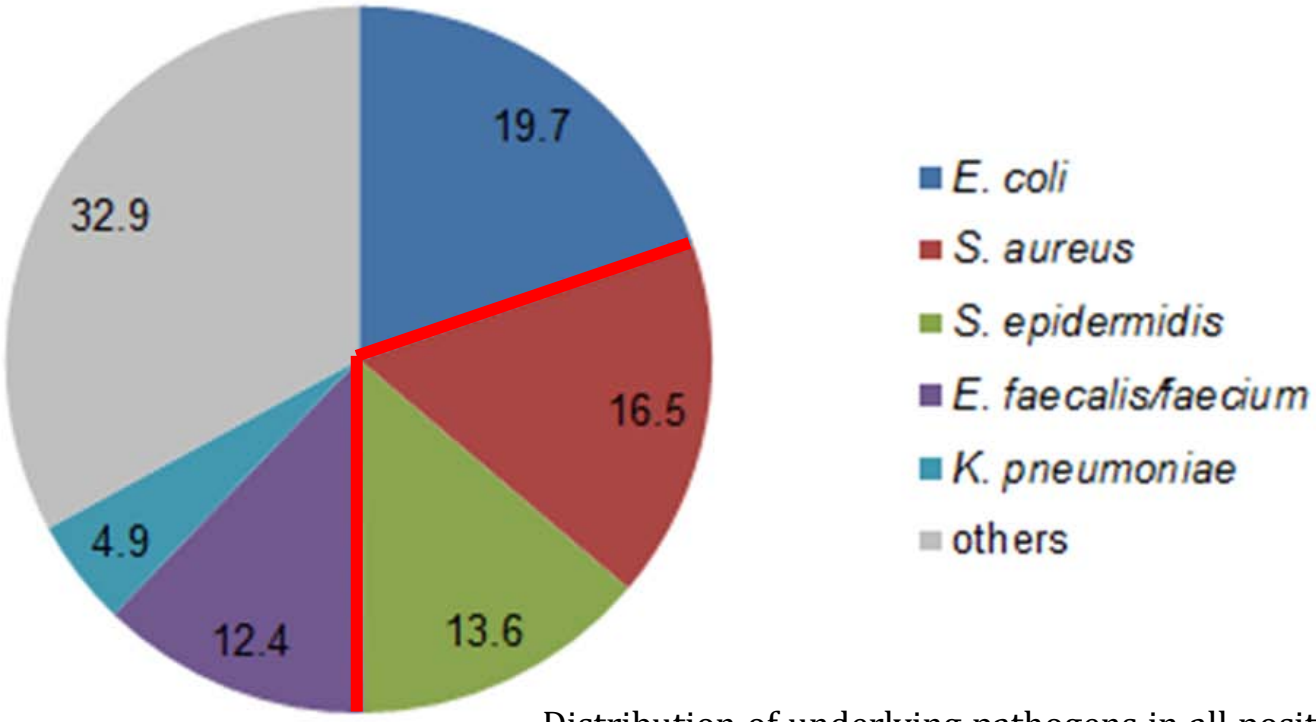
- 28,273 BC sets / 12 mon (May 2014 – April 2015) in **11** hospitals
- 16% positive, 7% clinically relevant positive



Results from the first 12-months report

- Distribution of pathogens -

- *Escherichia coli*, *Staphylococcus aureus*, *S. epidermidis* and enterococci were responsible for more than 60% of all BSIs

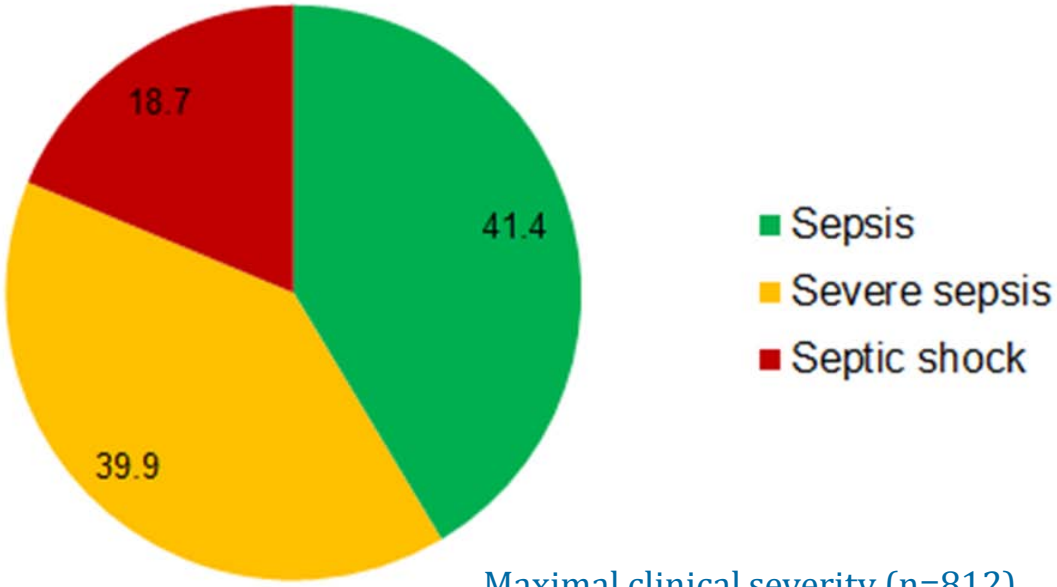


Distribution of underlying pathogens in all positive blood cultures deemed as clinically relevant (n=1,881)

Results from the first 12-months report

- Clinical severity -

- 812 patients with 1-6 positive BCs
- 60,8% nosocomial BSIs: 70,4% ward and 29,6% ICU patients
- ~60% with severe sepsis/septic shock

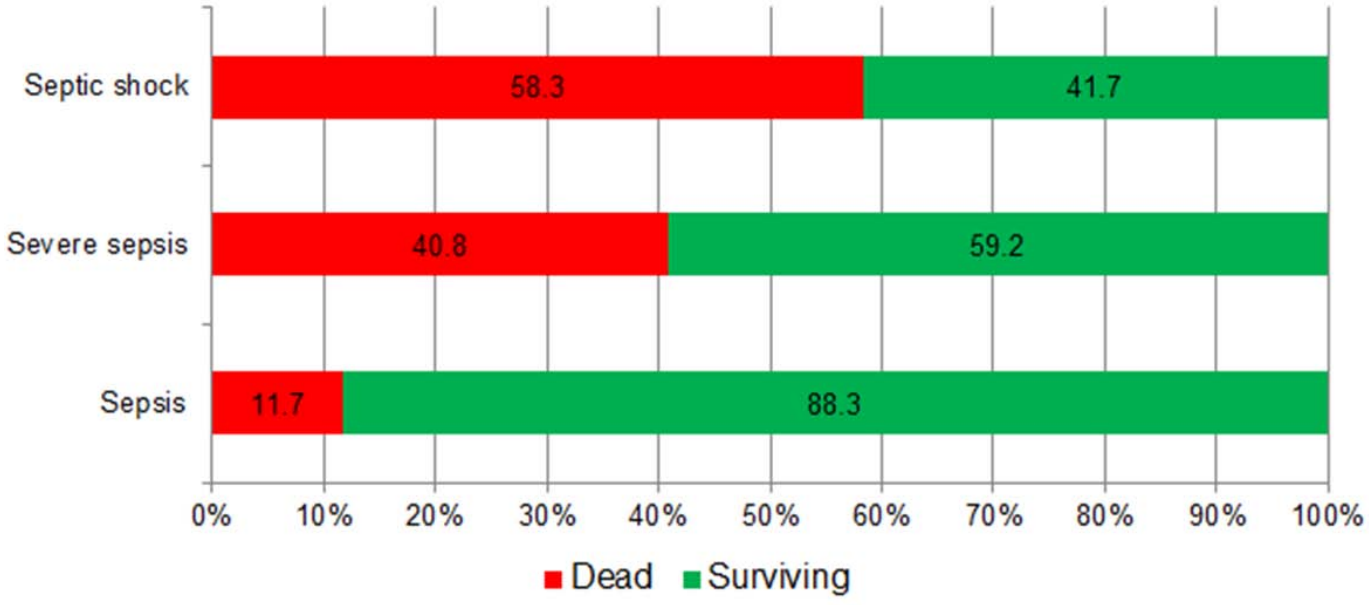


Maximal clinical severity (n=812)

Results from the first 12-months report

- Hospital mortality -

- Total: 23,3%



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Use of Electronic Health Records (EHRs) and Clinical Decision Support Systems (CDSSs) for Antimicrobial Stewardship

Use of Electronic Health Records (EHRs) and Clinical Decision Support Systems (CDSSs) for Antimicrobial Stewardship in the United States

	EHRs		CDSSs				
Feature	Epic	Cerner	TheraDoc (Premier)	SafetySurveillor (Premier)	QC PathFinder (Vecna)	Sentri7 (Pharmacy OneSource)	MedMined (CareFusion)
EHR integration	NA	NA	Yes	No	Yes	Yes	No
Treatment guidelines	Order sets	Order sets	Yes	No	No	Yes (via embedded hyperlinks)	No
Real-time alerts	Yes	Yes (with IT customization)	Yes	Yes	Yes	Yes	Yes
Delayed alerts[a]	Yes	No	No	Yes	Yes	Yes	Yes
Customizable alerts	Yes	Yes (with IT customization)	Yes	Yes	Yes	Yes	Yes
Clinical information	Yes	Yes	Yes	Yes	No	Yes	Yes
Infection control software	Yes	No	Yes	Yes	Yes	Yes	Yes
Institutional antibiogram	Yes	No	Yes	Yes	Yes	Yes	Yes
Unit antibiogram	Yes	No	Yes	Yes	Yes	Yes (available in June 2014)	Yes
Prescriber metrics	Yes	No	Yes	Yes	No	No	Yes
Patient outcome tracking and reporting capabilities	No	No	No	No	No	No	No
Product cost	++++	++++	++++	+++	+++	+++	+++

Abbreviations: +++, >$100K; ++++, >$500K; CDSS, clinical decision support system; EHR, electronic health record; IT, information technology; NA, not applicable.

[a] With the delayed-alert feature, alerts do not occur in real time but 2–3 times a day, depending on how data from the hospital warehouse are uploaded to the server.

"There is now an urgent need for a new generation of EHRs and CDSSs that can provide ASPs with patient outcomes data and that can play a role in improving patient outcomes."

Clinical Infectious Diseases 2014;59(S3):S122–33

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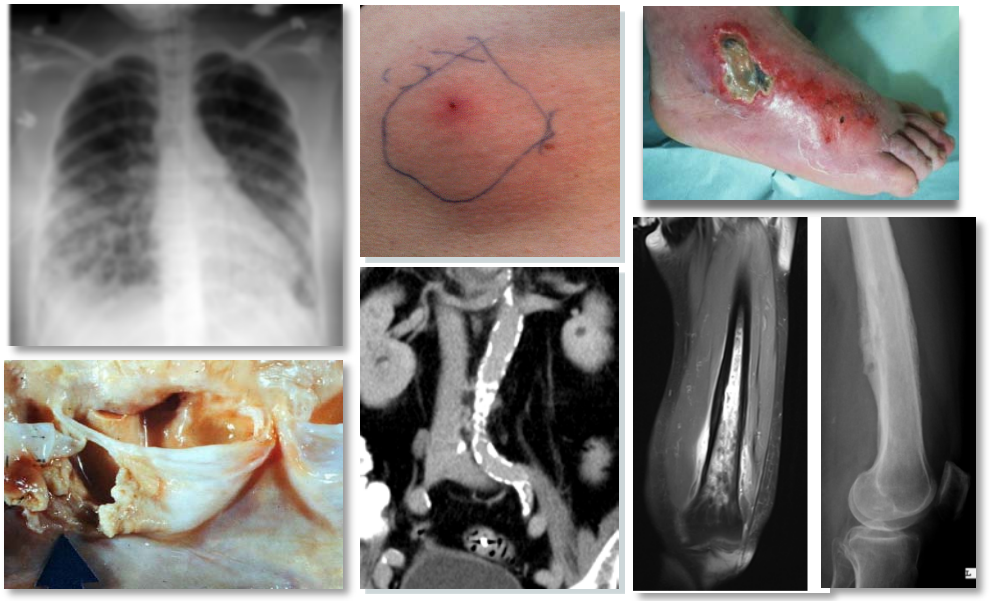
St. Aureus Bacteremia (SAB)

S. aureus - colonisation and infection

Colonisation on epithelial layers

Invasive und systemic infections

acute infection ⟶ chronic, recurrent infection



Kluytmans J *et al.*, Clin. Microbiol. Rev., 1997

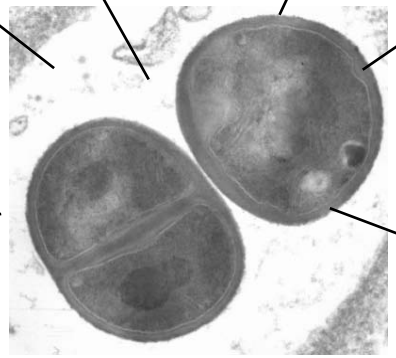
von Eiff C *et al.*, N Engl J Med, 2001

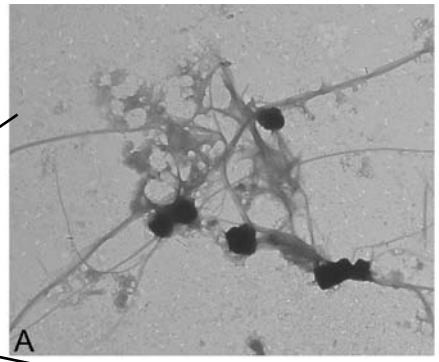
S. aureus – virulence factors

Secreted toxins and superantigens
i.e. TSST-1,
Enterotoxins,
pore-forming toxins
i.e. a-Toxin, PVL

Enzyms
z.B. Proteases,
Lipases,
Elastases

Cell wall components
Lipoteichon acid,
Peptidoglycans





Biofilm formation

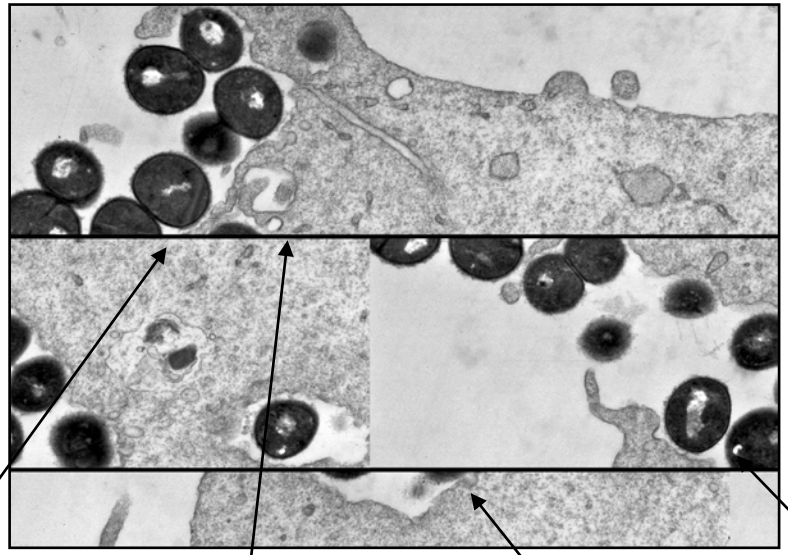
Other secreted components i.e.
Phenol-soluble modulins

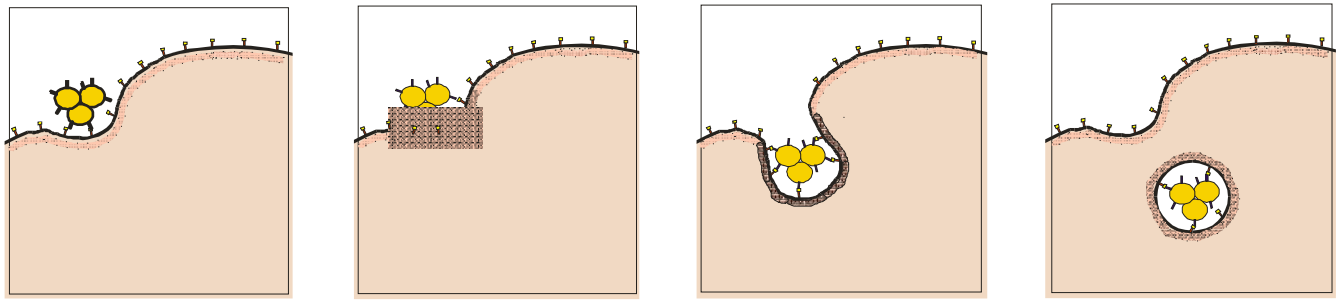
Capsule

- **Characteristics of virulence factors varys among clinical *S. aureus* isolates**
- **Expression of virulence factors is driven by regulatory systems, i.e. Agr, SarA, SigB.**

Lowy FD *et al.*, N Engl J Med, 1998

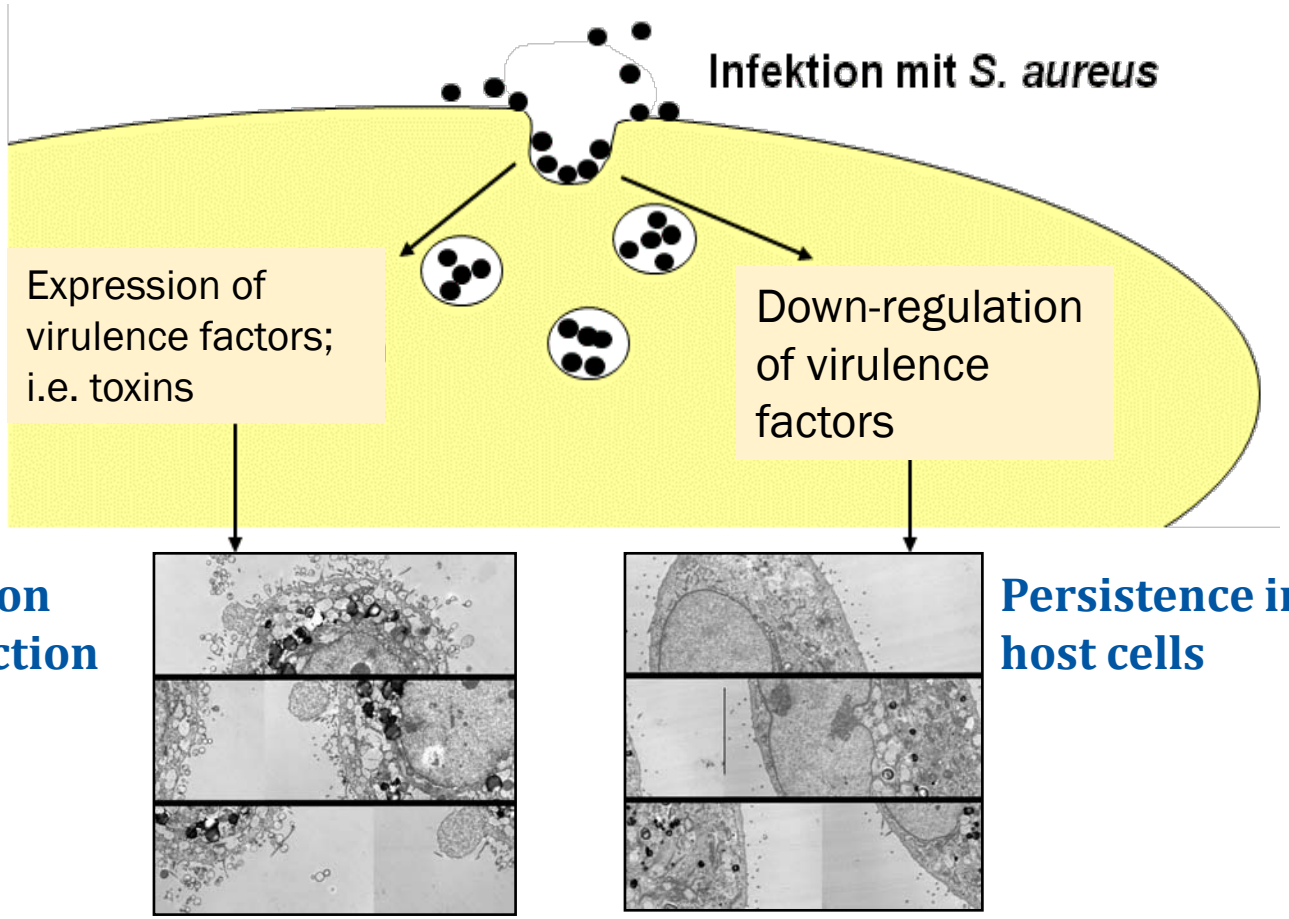
S. aureus - invasion of host cells





Haslinger-Löffler B et al. Kidney Int 2006

Staph aureus - Post-invasion effects



Inflammation and destruction

Persistence in intact host cells

Löffler et al. Z. Herz-Thorax-Gefäßchir 2012

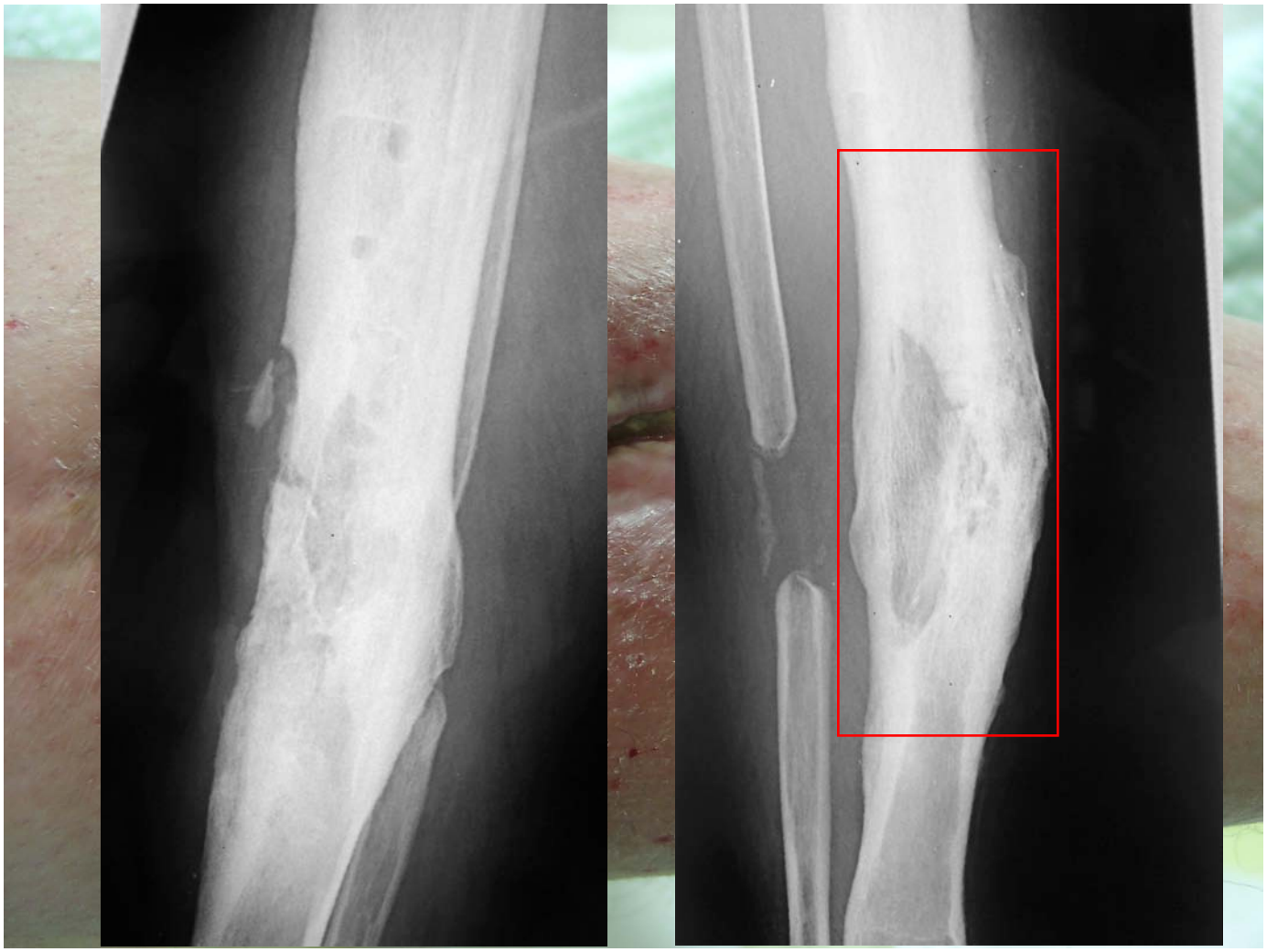
Staph aureus- wild-type vs SCV phenotype

Wild-Type phenotype

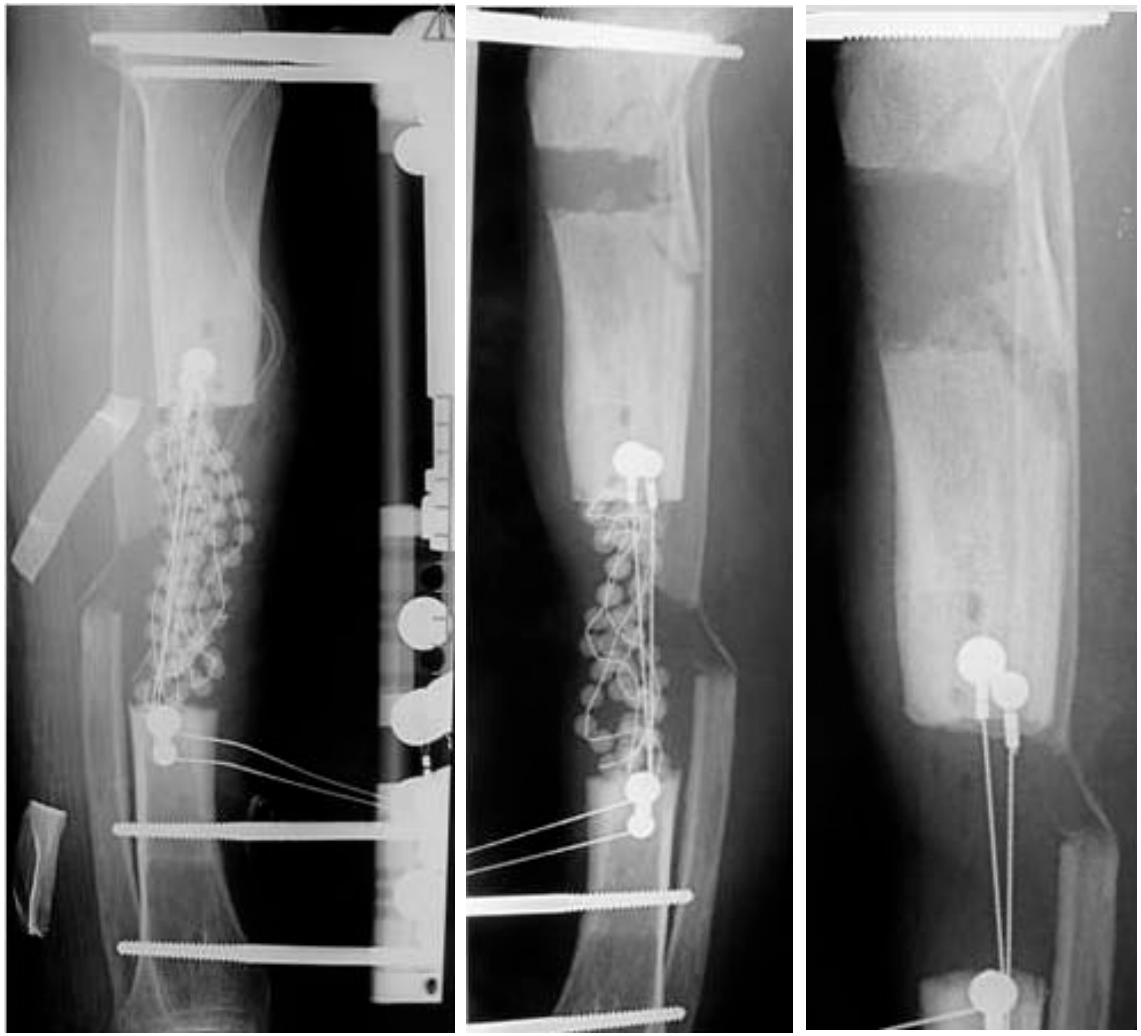
Small Colony Variant (SCV) phenotype

- **Occurence of is associated with chronic infections (i.e. osteomyelitis).**
- **SCVs grow slowly and exhibit reduced metabolism**
- **Mutants in molecular transport systems exhibit SCV-phenotype**
- **Clinical SCVs are not stabile and may re-convert to wild-type phenotype**

Chronic *S. aureus* osteomyelitis

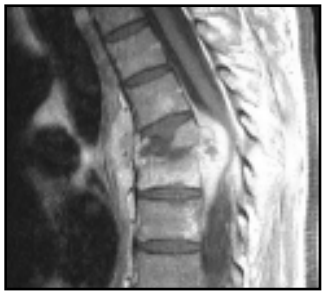


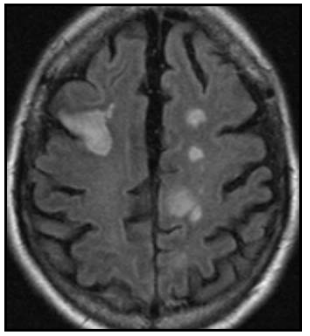
Chronic *S. aureus* osteomyelitis

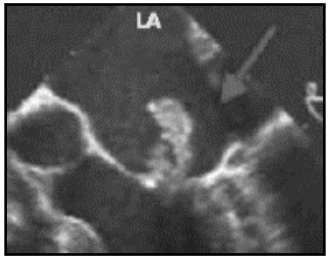


SAB – a special clinical entity

1. **SAB is common**
   - Incidence 15-35/100.000/yr
   - Jena: 220/yr (15% MRSA)
2. **SAB has a high mortality despite ABx**
   - until 1960 ~80%
   - from 1960 ~ 30%
   - 1. BC → death: ~ 8 days
3. **SAB with complications**
   - Secondary foci 30 – 40%
   - Acute renal failure 20%
   - Recurrence 10%







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Case report: 78 yr, male

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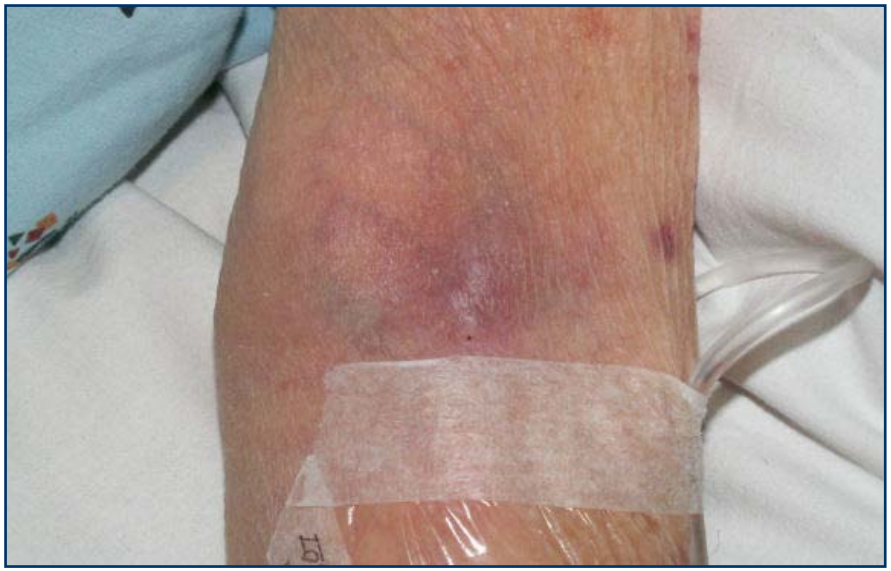
Staph aureus bacteremia

Staph aureus bacteremia

Day 10

- Reknowned scientist in chemistry
- CLL, NYHA II, MI II-III, cardiac pacemaker, chronic RF
- Herpes zoster: 10 days iv Acyclovir (PVC)



Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

Staph aureus bacteremia

Day 12-14

- Reknowned scientist
- CLL, NYHA II, MI II-III, cardiac pacemaker, chronic RF
- Herpes zoster: 10 days iv Acyclovir (PVC)
- 2 days after discharge fever & chills
- Re-admission: surgical abscess drainage, no ABx

Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

Staph aureus bacteremia

Day 12-14

- Reknowned scientist
- CLL, NYHA II, MI II-III, cardiac pacemaker, chronic RF
- Herpes zoster: 10 days iv Acyclovir (PVC)
- 2 days after discharge fever & chills
- Re-admission: surgical abscess drainage, no ABx
- 2 days later: fever, confusion, BC cultures taken, NO ABx

Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

Staph aureus bacteremia

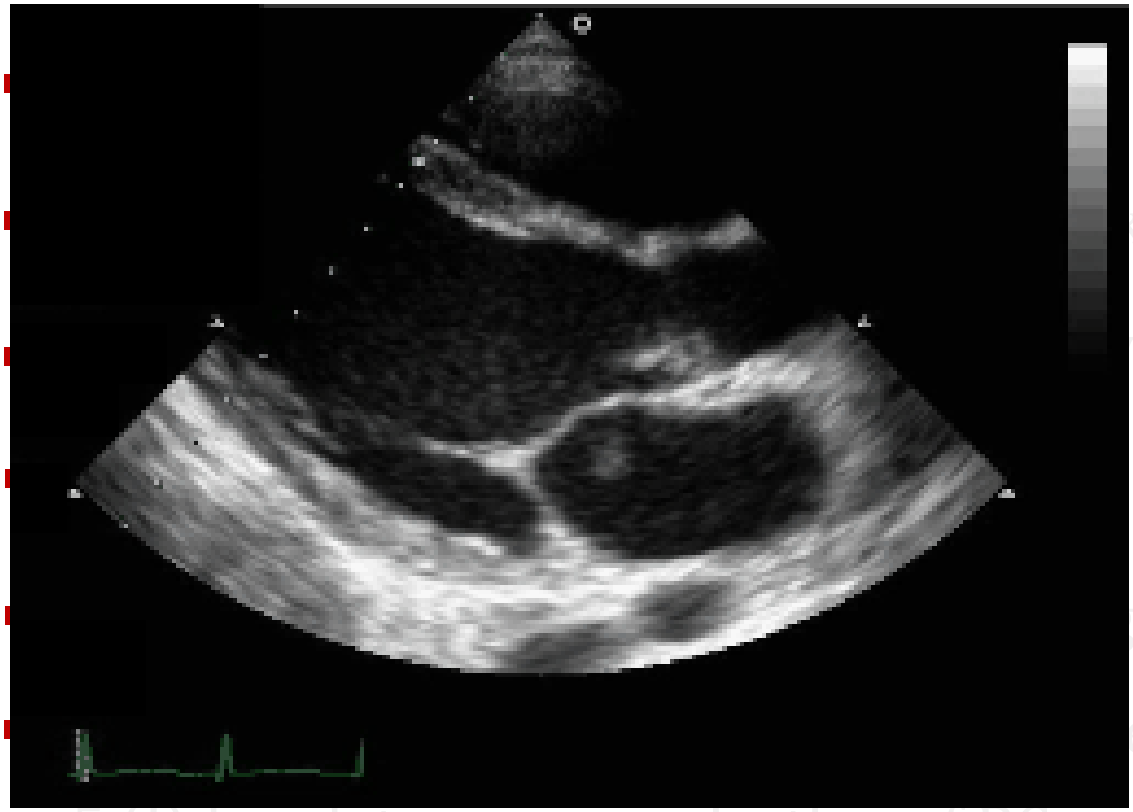
Day 19

- Reknowned scientist
- CLL, NYHA II, MI II-III, cardiac pacemaker, chronic RF
- Herpes zoster: 10 days iv Acyclovir (PVC)
- 2 days after discharge fever & chills
- Re-admission: surgical abscess drainage, no ABx
- 2 days later: fever, confusion, BC cultures taken, NO ABx
- 5 (!)days later communication of BC results: SAB, Abx started

Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

Staph aureus bacteremia

Day 20



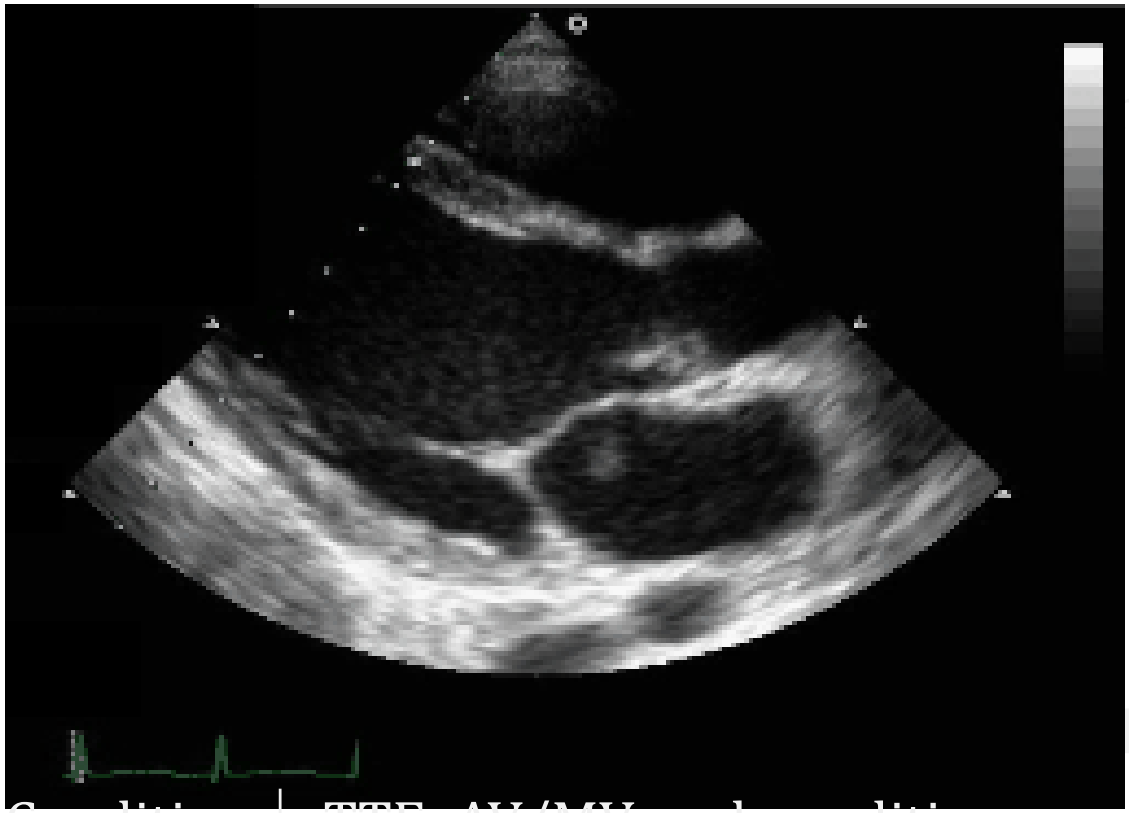
- Condition ↓, TTE: AV/MV-endocarditis, pacemaker wire with vegetations

Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

Staph aureus bacteremia

Day 30

- Reknowned scientist
- , chronic RF
- no ABx
- taken, NO ABx
- ts: SAB, Abx started
- Condition ↓, TTE: AV/MV-endocarditis, pacemaker wire with vegetations



- MK-replacement/ECMO, MOF, exitus day 10 post OP

Frosinski J, Brunkhorst FM. Dtsch Med Wochenschr 2013; 1380: 1723–1726

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Clinical studies

Quasi-experimental study in 12 tertiary Spanish hospitals

MAJOR ARTICLE

Impact of an Evidence-Based Bundle Intervention in the Quality-of-Care Management and Outcome of *Staphylococcus aureus* Bacteremia

Luis E. López-Cortés,[1,a] Maria Dolores del Toro,[1,2] Juan Gálvez-Acebal,[1,2] Elena Bereciartua-Bastarrica,[3] María Carmen Fariñas,[4] Mercedes Sanz-Franco,[5] Clara Natera,[6] Juan E. Corzo,[7] José Manuel Lomas,[8] Juan Pasquau,[9] Alfonso del Arco,[10] María Paz Martínez,[11] Alberto Romero,[12] Miguel A. Muniain,[1,2,14] Marina de Cueto,[1,2] Álvaro Pascual,[1,2,13] and Jesús Rodríguez-Baño;[1,2,14] for the REIPI/SAB group[b]

Clinical Infectious Diseases 2013;57(9):1225–33

Quality-of-care indicators

- Control blood cultures (48-72h)
- Source control (incl. TEE)
- Small spectrum ß-lactam i.v. antibiotics in case of MSSA
- Adequate vancomycin-plasma concentrations in case of MRSA
- Adequate treatment duration (at least 14 days)
- Combination therapy in selected cases (Rifampicin, Fosfomycin)

Clinical Infectious Diseases 2013;57(9):1225–33

Uncomplicated vs complicated bacteremia (ISDA)

uncomplicated bacteremia

- exclusion of endocarditis;
- no implanted prostheses;
- follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA;
- defervescence within 72 h of initiating effective therapy;
- no evidence of metastatic sites of infection

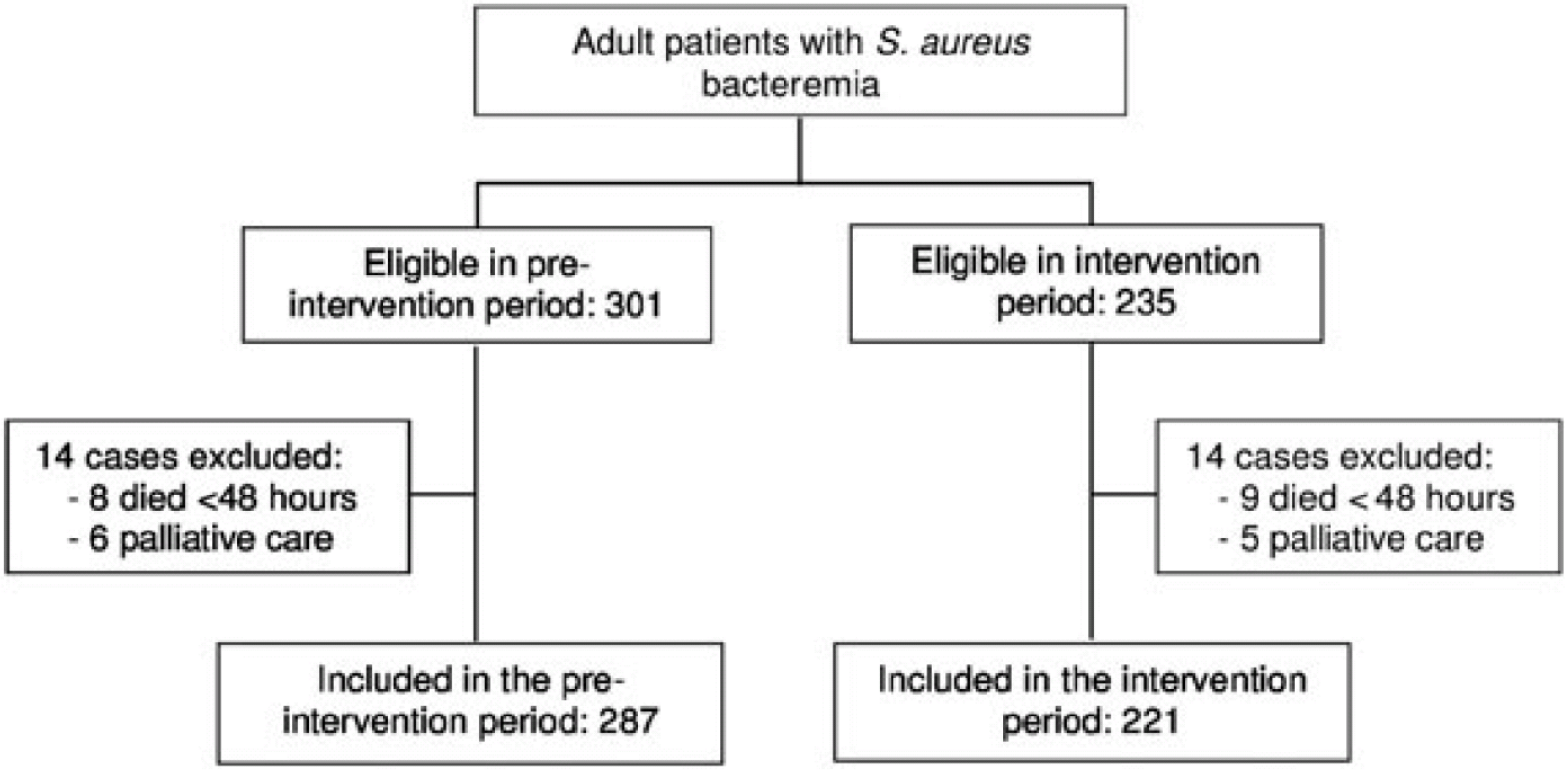
complicated bacteremia

- patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *StaphylococcusAureus* Infections in Adults and Children

Clin Infect Dis. (2011) doi: 10.1093/cid/ciq146

Infectious Diseases Consultation in *SAB*



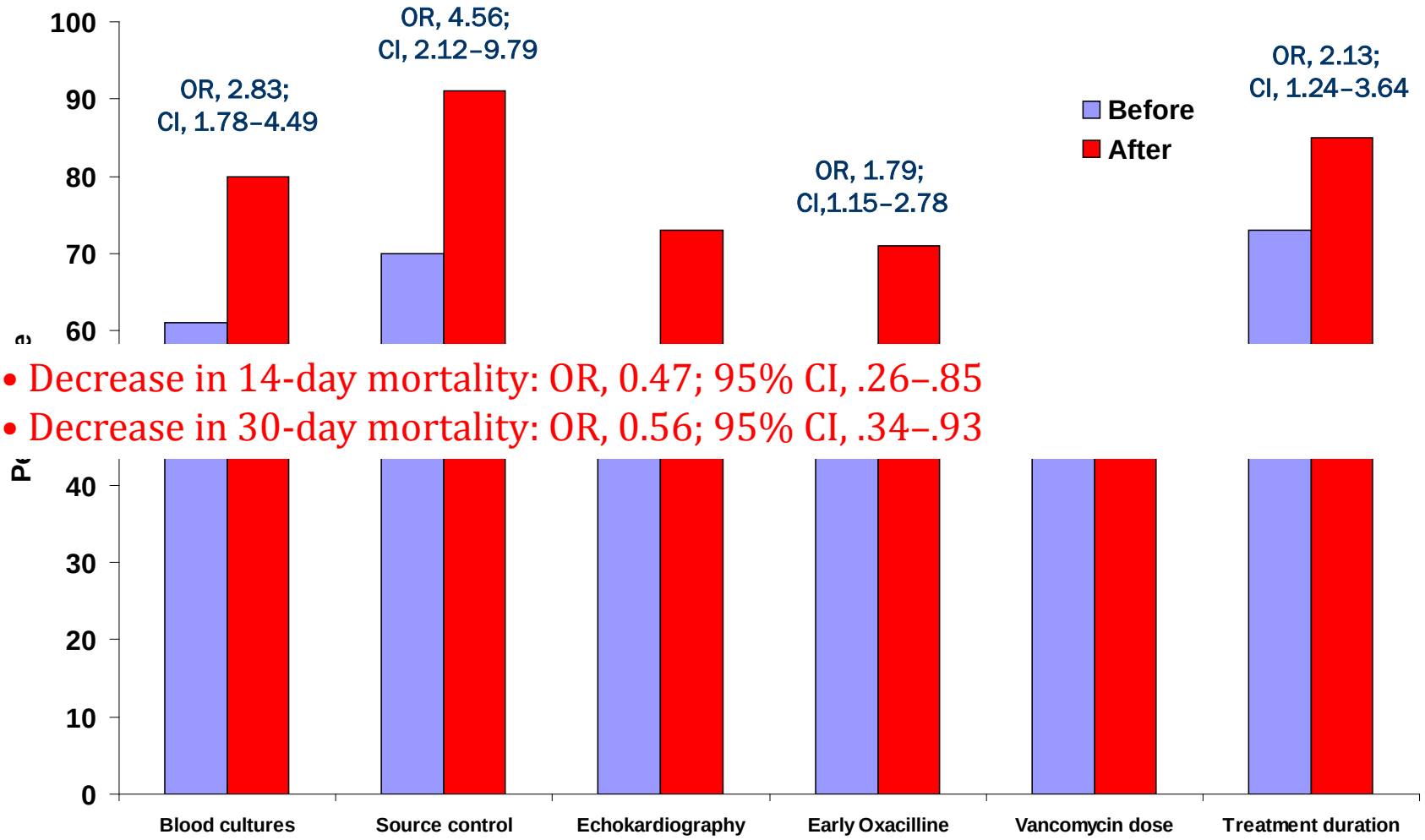
Clinical Infectious Diseases 2013;57(9):1225–33

Infectious Diseases Consultation in *SAB*

Variable	All Patients (n = 508)	Preintervention (n = 287)	Intervention (n = 221)	*P* Value
Median age, y, (IQR)	67 (55–76)	67 (55–75)	66 (56–77)	.63
Female sex	170 (33.5)	89 (31)	81 (36.7)	.18
Comorbidities				
Diabetes mellitus	148 (29.1)	83 (28.9)	65 (29.4)	.90
Chronic pulmonary disease	69 (13.6)	39 (13.6)	30 (13.6)	.99
Hemodialysis	46 (9.1)	21 (7.3)	25 (11.3)	.12
Malignancy	122 (24)	73 (25.4)	49 (22.2)	.39
Chronic liver disease	60 (11.8)	32 (11.1)	28 (12.7)	.59
Immunosuppression	73 (14.4)	42 (14.6)	31 (14)	.84
Intravenous drug abuse	9 (1.8)	7 (2.4)	2 (0.9)	.19
Endocarditis-predisposing condition	72 (14.2)	42 (14.6)	30 (13.6)	.73
Charlson index ≥2	331 (65.3)	191 (66.8)	140 (63.3)	.42
Pitt score >2	110 (21.7)	64 (22.3)	46 (22.2)	.79
Acquisition				
Hospital-acquired infection	292 (57.5)	165 (57.5)	127 (57.5)	.99
Healthcare-related bacteremia	132 (26)	73 (25.4)	59 (26.7)	.74
Source of bacteremia				
Vascular catheter	197 (38.8)	100 (34.8)	97 (43.9)	.04
Unknown source	172 (33.9)	95 (33.1)	77 (34.8)	.68
Skin and/or soft tissue	53 (10.4)	38 (13.2)	15 (6.8)	.02
Respiratory tract	25 (4.9)	13 (4.5)	12 (5.4)	.22
Osteoarticular	31 (6.1)	21 (7.3)	10 (4.5)	.19
High-risk source[a]	32 (6.3)	18 (6.3)	14 (6.3)	.97
Complicated bacteremia	238 (46.9)	140 (48.8)	98 (44.3)	.32
MRSA	102 (20.1)	57 (19.9)	45 (20.4)	.89
Endocarditis (primary and secondary)[b]	22/180 (12.2)	11/83 (13.3)	11/97 (11.3)	.69
Appropriate empirical therapy	125 (80.1)	65 (75.6)	60 (85.7)	.12
Severe sepsis or septic shock	120 (22.4)	71 (24.2)	46 (20.9)	.51
Unfavorable course[c]	179 (35.2)	96 (33.4)	83 (37.6)	.33

Clinical Infectious Diseases 2013;57(9):1225–33

Adherence to quality-of-care indicators



- Decrease in 14-day mortality: OR, 0.47; 95% CI, .26–.85
- Decrease in 30-day mortality: OR, 0.56; 95% CI, .34–.93

Clinical Infectious Diseases 2013;57(9):1225–33

Staph aureus bacteremia

> That's a big deal in the current era of cost containment and evidence-based healthcare and a strong reminder that gee-whiz technologies and this year's wonder drug are no replacement for expert care
>
> - T. Lahey, 2013

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Metaanalysis

Journal of Infection (2016) 72, 19–28

ELSEVIER

BIA British Infection Association

www.elsevierhealth.com/journals/jinf

Infectious disease consultation for *Staphylococcus aureus* bacteremia – A systematic review and meta-analysis

Monique Vogel [a], Roland P.H. Schmitz [a], Stefan Hagel [c,d], Mathias W. Pletz [c,d], Nico Gagelmann [a], André Scherag [c,e], Peter Schlattmann [f], Frank M. Brunkhorst [a,b,c,*]

Journal of Infection (2016) 72, 19-28

Background

- SAB incidence: 15 – 40 / 100 000 p.a.
- SAB case fatality rate: 15 – 25 %
- frequent complications → high morbidity
- **recent data suggest improved management and survival by Infectious Disease Specialists' consultation**
- **published studies with moderate to small sample sizes**

Methods

Systematic search

- Medline
- The Cochrane Library
- Web of Science

} **from inception to 31st July 2014**

3 investigators searched/extracted data independently

Meta-analysis

- implemented R package META
  - Meta-analysis & plots: “metabin” & “forest.meta”
  - Bias & sensitivity: “metabias” & “metainf”

Definitions

Inclusion criteria

- **P**opulation: patients with SAB
- **I**ntervention: at least 1 formal IDC
- **C**ontrol: no IDC
- **O**utcome: mortality until day 30 or 90
  and/or Quality of Care Indicators

Definitions

Quality of Care Indicators

- appropriate agent for antibiotic therapy
- appropriate duration of antibiotic therapy
- follow-up blood cultures
- echocardiography

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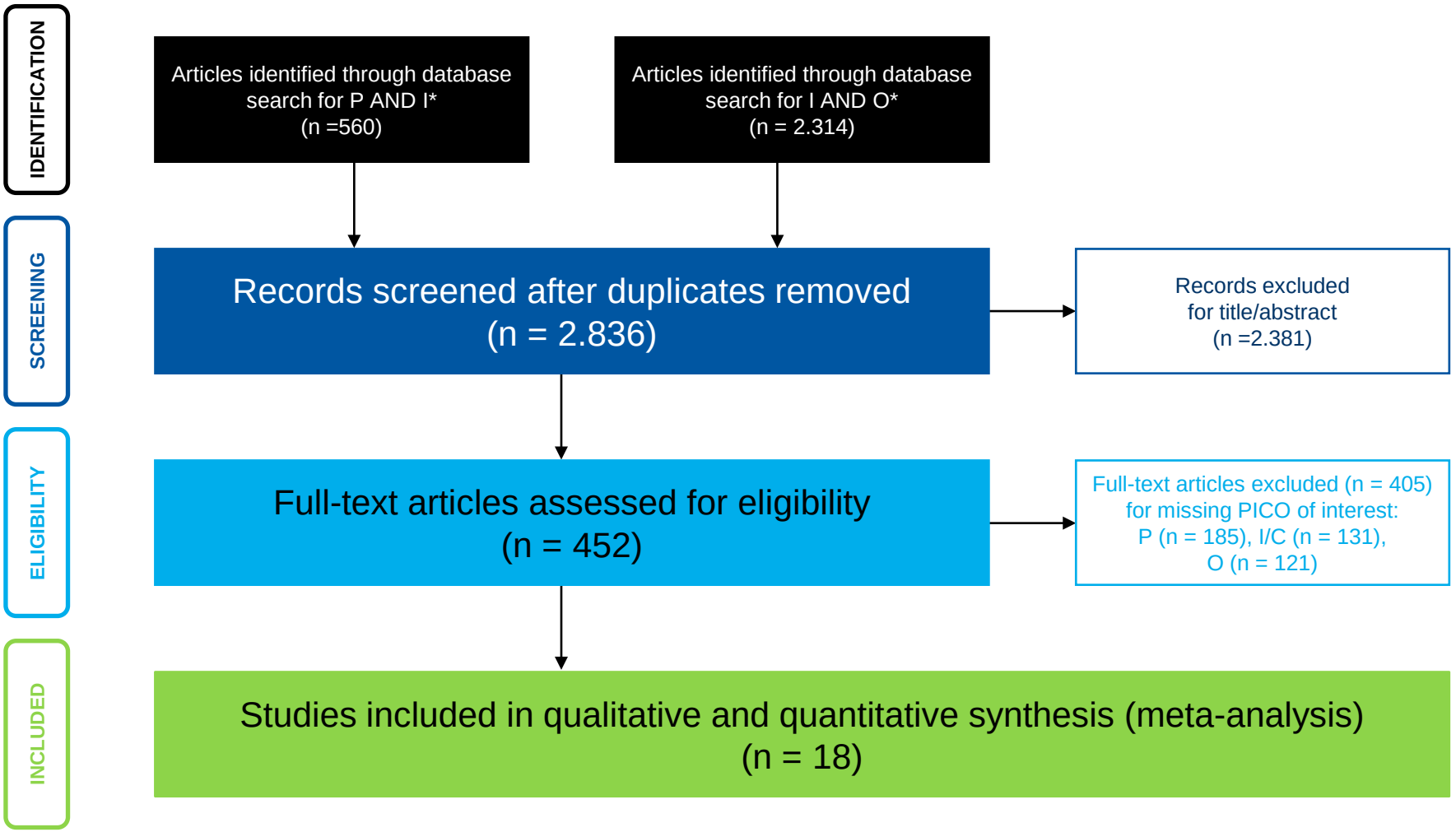
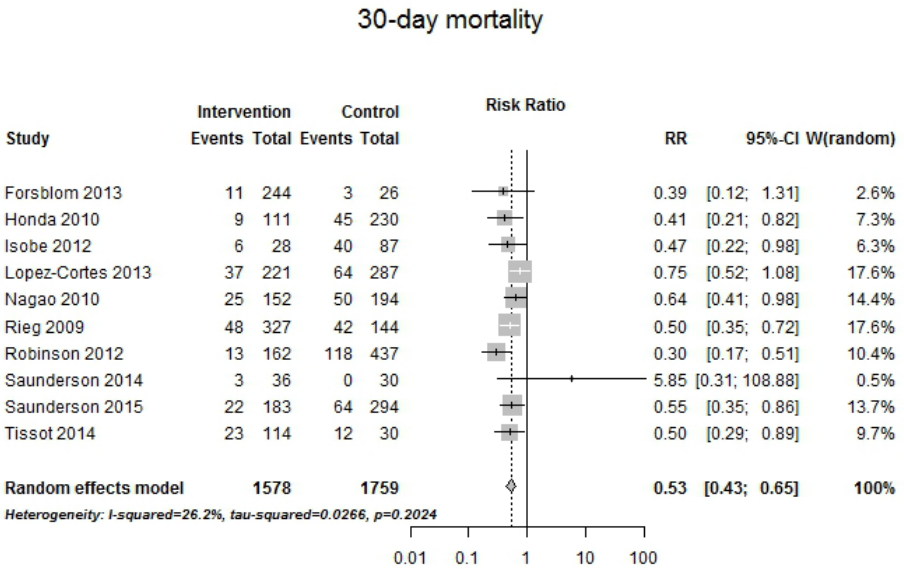
Results

Study identification

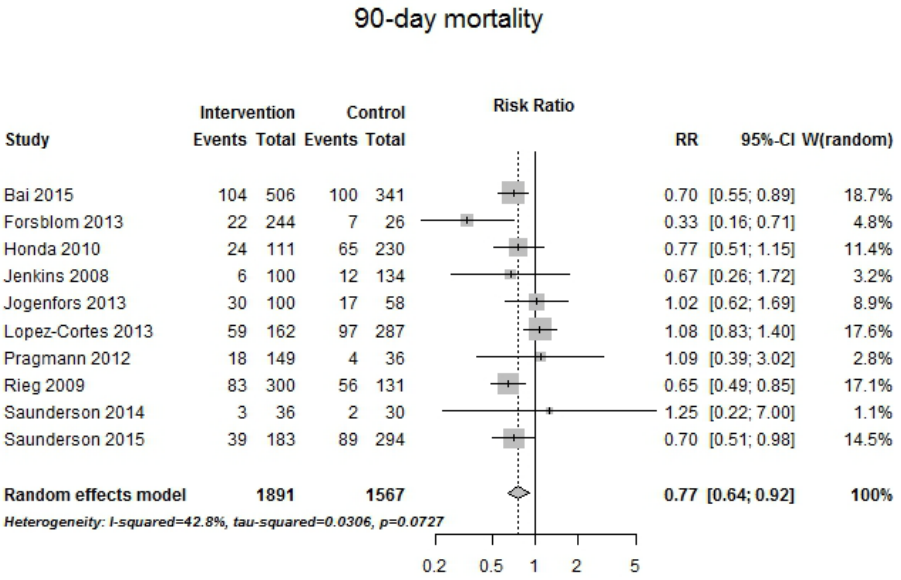


Mortality of SAB with vs. without IDC



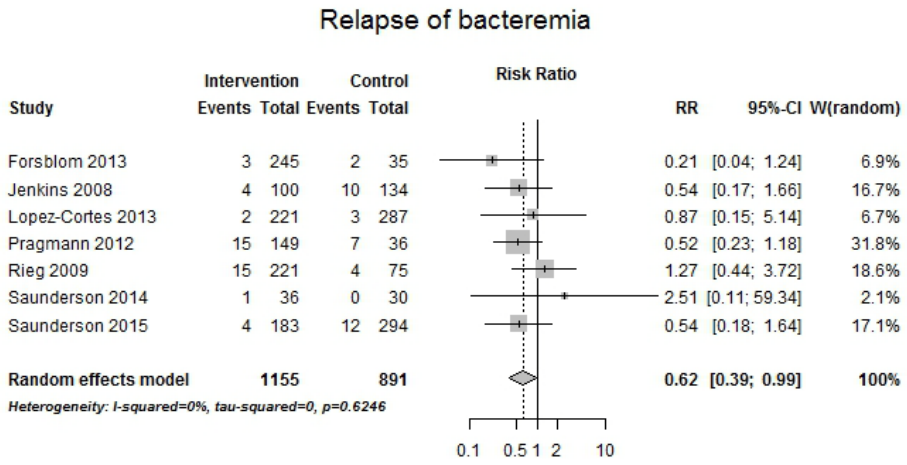
- overall 30-day case fatality rates differ significantly
  - ✓ **12.39 % for IDC group**
  - ✓ **26.07 % for control**
- RR 0.53 [95% CI 0.43 – 0.65]

Mortality of SAB with vs. without IDC



- overall 90-day case fatality rates differ significantly
  - ✓ **17.45 % for IDC group**
  - ✓ **23.49 % for control**
- RR 0.77 [95% CI 0.64 – 0.92]

Relapse of SAB with vs. without IDC



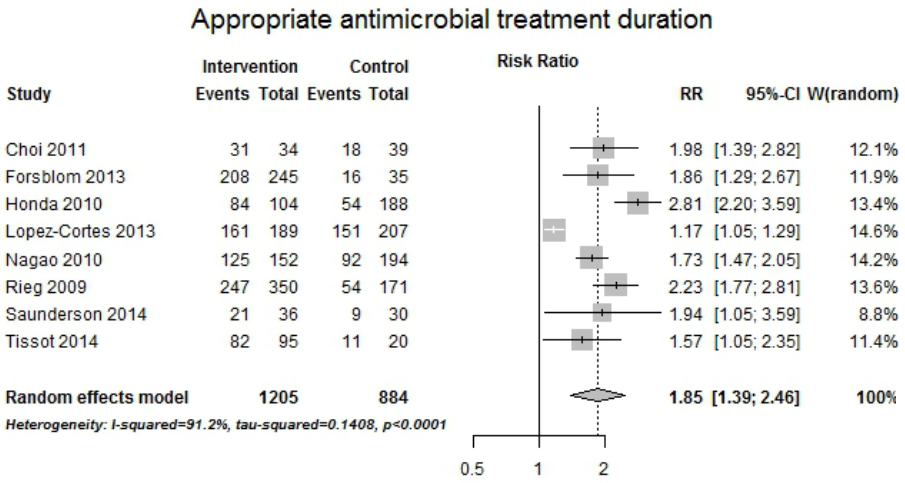
- Relapse rates

  differ significantly

- RR 0.62

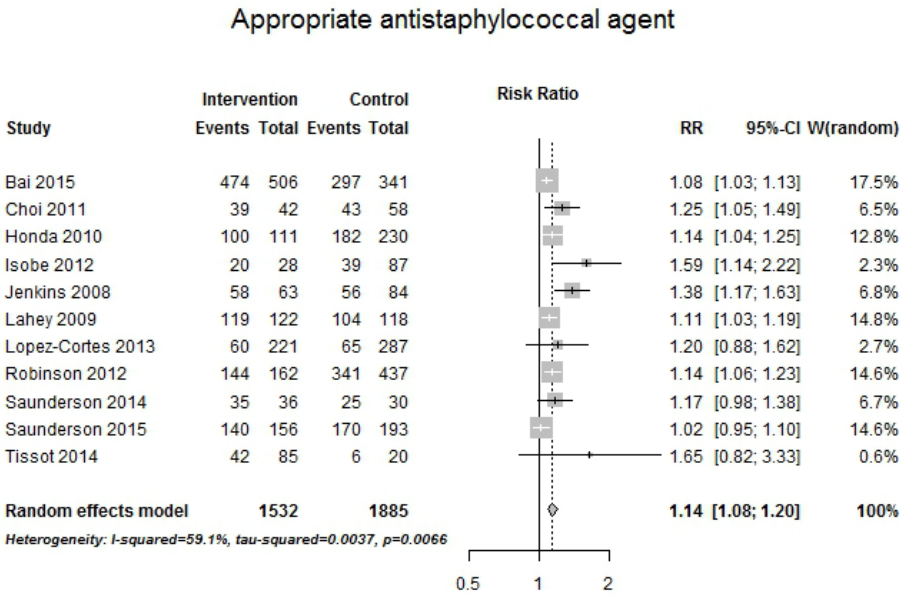
  [95% CI 0.39 – 0.99]

Appropriate antibiotic therapy for SAB

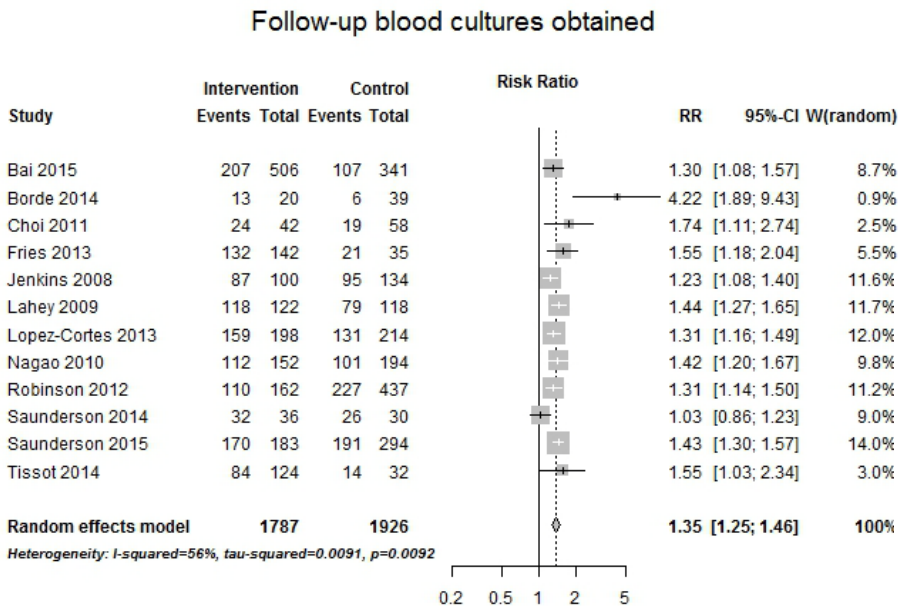


- AB duration: RR 1.85 [95% CI 1.39 – 2.46]
- AB agent: RR 1.14 [95% CI 1.08 – 1.20]

- Rates of appropriate antibiotic therapy differ significantly

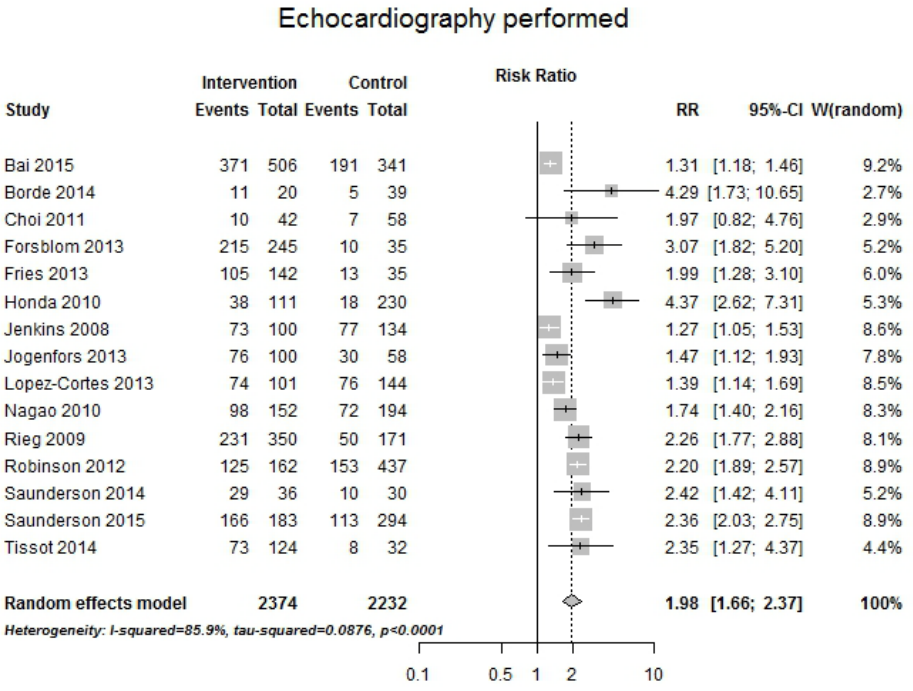


Quality of Care Indicators for SAB



- Follow-up BK: RR 1.35 [95% CI 1.25 – 1.46]
- Echo: RR 1.98 [95% CI 1.66 – 2.37]

- Rates of Quality of Care Indicators differ significantly



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Conclusions

Conclusion

- Evidence based clinical management enforced by IDC improves outcome of patients with SAB
- well-designed randomized controlled multicentre trials are needed to confirm these findings:
- *Study on the utility of a statewide counseling program for improving outcomes of patients with staphylococcal bacteremia in Thuringia - a cluster-randomized cross-over trial (SUPPORT)*

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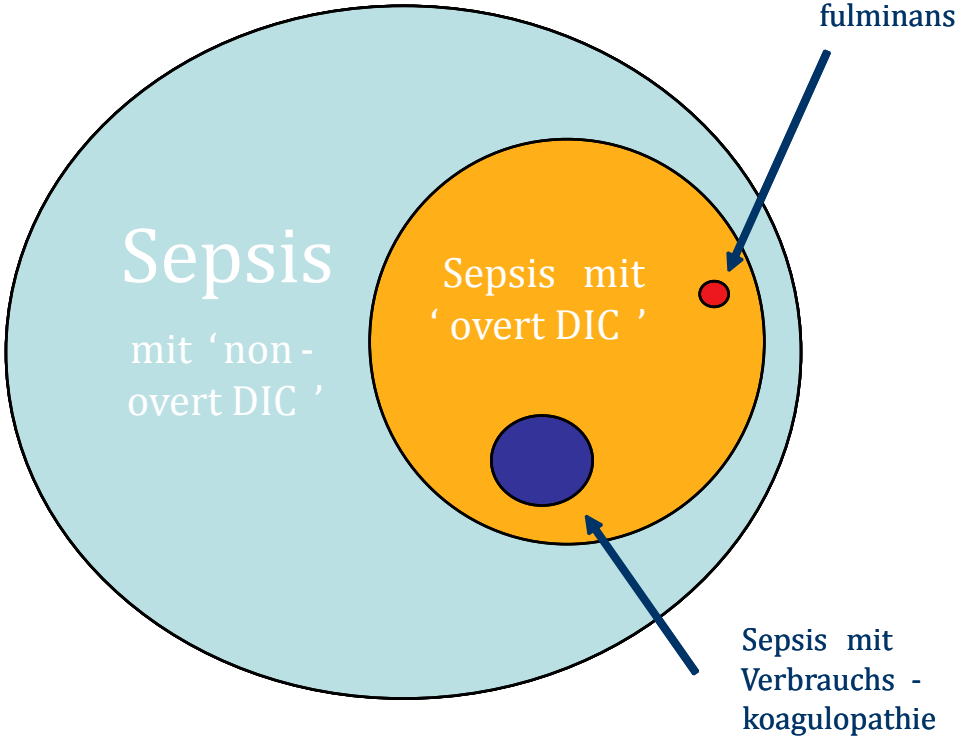
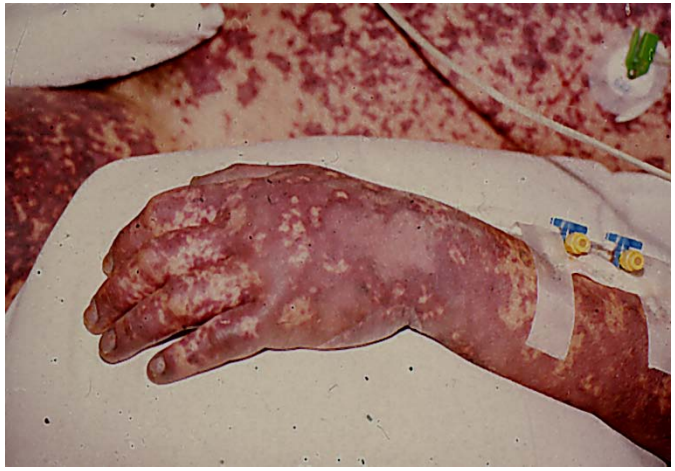
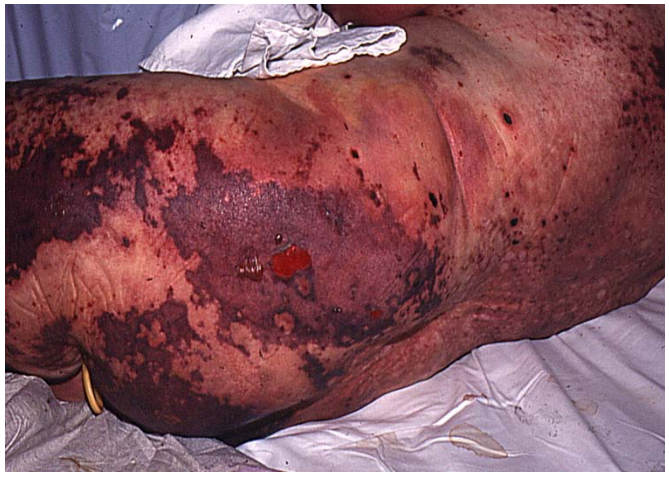
Sepsis Associated Purpura Fulminans (SAPF)

Severe disturbances in hemostasis are rare in severe sepsis







Mod. nach Dempfle, C.-E.

National SPLEEN-OFF Study

Ambulant erworbene schwere Sepsis oder septischer Schock

MILZ ⊖ = FALL

MILZ ⊕ = KONTROLLE

SPLEEN OFF ... OPSI REGISTER

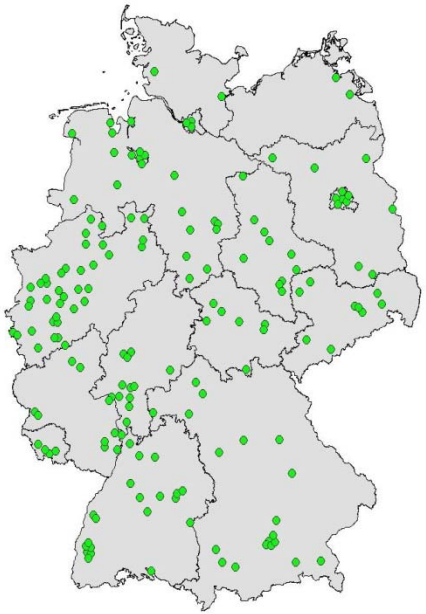
TAG 0:
- Klinik
- Mikrobiologie
- Risiko-/ Prognosefaktoren
- Pneumokokken-Antikörper

ITN:
- Sepsisschwere

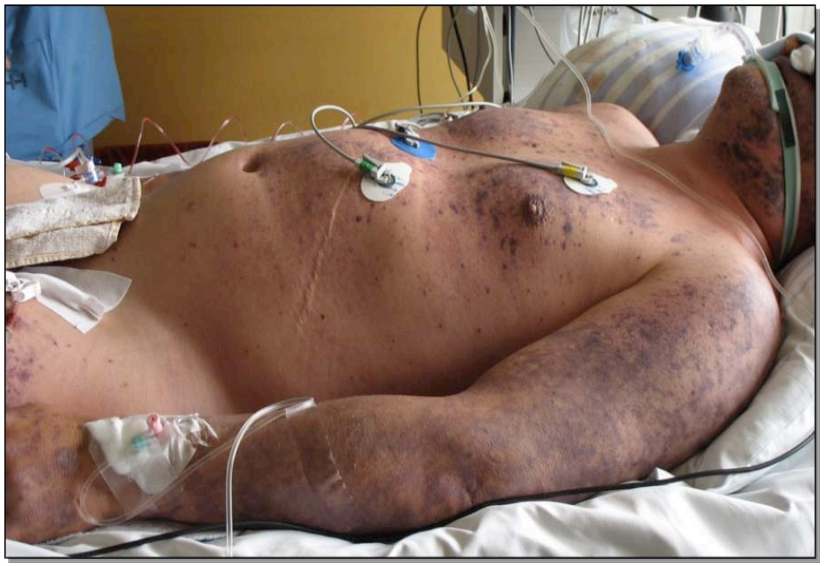
TAG 28:
- 28-Tage Letalität
- ITS- / Kranken-hausverweildauer

2 Jahre
- Letalität und Mortalität
- Infektanfälligkeit
- B-Zell-Immunologie

Aktive SPLEEN OFF Studienzentren



Stand 08/2011



SPLEEN OFF Studie

Studienzentrale Freiburg
Zentrum für Chronische Immundefizienz (CCI)
Universitätsklinikum Freiburg
☎ 0761-270 77880
Fax 0761-270 73770
✉ spleen-off@uniklinik-freiburg.de
www.spleen-off.org
www.cci.uniklinik-freiburg.de

SepNet Büro Jena
Zentrum für Sepsis und Sepsisfolgen (CSCC)
Universitätsklinikum Jena
☎ 03641-9 3233-81
Fax 03641-9 3233-87
✉ sepsis@med.uni-jena.de
www.sepsis-gesellschaft.de

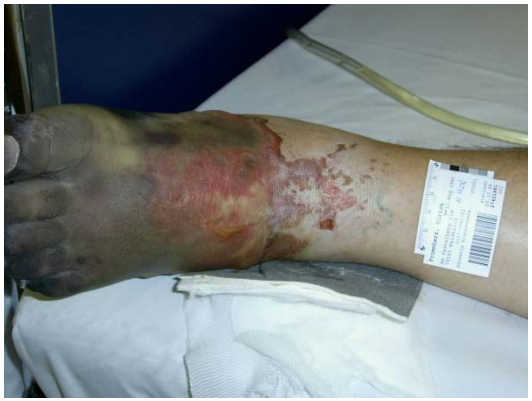
GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

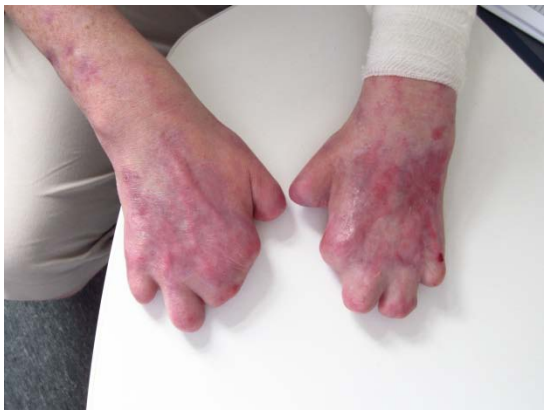
Kompetenznetz Sepsis

Centrum für Chronische Immundefizienz

OPSI – Overwhelming Post-Splenectomy Infection (OPSI)

- First described 50 yrs ago
- Lifetime risk ≈ 2 - 5% (?)
- Case fatality rate ≈ 50%
- Pneumococcei leading pathogen
- Pathogenesis unclear





National SPLEEN-OFF Study

Table 1. Baseline characteristics including vaccination history of cases and controls.

Characteristic	Asplenia (n=52)	Controls (n=52)	p value
Demographics and general risk factors			
Age*	55 (44-66)	61 (45-69)	**0·002**
Male sex	29 (56%)	29 (56)	1·000
BMI*	24 (22-27)	28 (23-34)	**0·004**
Current smoking[a]	14 (27%)	18 (35%)	0·481
Alcohol use[b]	6 (12%)	11 (21%)	0·424
Comorbidity			
Charlson's comorbidity index*	2 (0-4)	2 (0-3)	0·471
History of malignancy	20 (38%)	9 (17%)	**0·019**
Active neoplastic disease	6 (12%)	3 (6%)	0·727
Immunosuppressive therapy[c]	5 (10%)	2 (4%)	0·453
Antineoplastic chemotherapy[d]	4 (8%)	1 (2%)	0·375
Vaccination status			
Pneumococcal vaccine			**<0·001**
- any time[e]	22 (42%)	4 (8%)	
- past 5 years	11 (21%)	4 (8%)	**0·092**
Meningococcal vaccine (any time)[f]	3 (6%)	0 (0%)	0·250
Haemophilus influenzae vaccine (any time)	6 (12%)	0 (0%)	**<0·001**
Influenza vaccine (previous season)	6 (12%)	12 (23%)	0·302
unknown	5 (10%)	5 (10%)	1·000
Antibiotic prophylaxis	3 (6%)	4 (8%)	1·000

Table 4 Infection focus, sepsis severity, and outcomes.

Parameter	Asplenia (n=52)	Controls (n=52)	p value
Infection focus, n (%)[a]			
Primary bacteremia (no site)	6 (12%)	0 (0%)	**0·031**
Respiratory tract	21 (40%)	27 (52%)	0·307
Intraabdominal	13 (25%)	8 (15%)	0·267
Urinary tract	1 (2%)	5 (10%)	0·219
Central nervous system	4 (8%)	3 (6%)	1·000
Skin / soft tissue	0 (0%)	6 (12%)	**0·031**
Other / not specified	7 (13%)	3 (6%)	0·727
Sepsis severity on admission			
APACHE II Score*[b]	23 (16-29)	25 (19-33)	**0·049**
SOFA Score*[c]	10 (8-13)	11 (8-14)	0·499
Metabolic acidosis, n (%)[d]	34 (65%)	37 (71%)	0·648
Procalcitonin level (ng/ml)*	34 (3-98)	15 (2-54)	0·430
Lactate (mmol/l)*	4·9 (1·9-10·1)	2·8 (1·6-6·4)	0·229
Purpura fulminans, n (%)	10 (19%)	3 (5%)	**0·016**
Outcomes			
Days on ICU**	13 (3-23)	18 (11-25)	0·753
Days in hospital**	29 (26-32)	31 (26-36)	0·733
Days on ventilator**	6 (1-11)	12 (7-16)	0·243
7-day mortality, n (%)[e]	11 (22%)	6 (12%)	0·302
28-day mortality, n (%)[f]	18 (38%)	18 (38%)	1·000

The median interval between splenectomy and OPSI onset was 5·75 years (interquartile range, 1-18·25 years), with a range between one month and 50 years.

Theilacker C, Brunkhorst FM, Kern W et al. Clinical Infectious Diseases 2016 (in press)

Vaccinations in asplenic persons

Impfplan bei Asplenie	Bitte Aktualisierungen unter www.asplenie-net.org beachten		(Stand 11/2015)
Alter	**Grundimmunisierung**	**1. Auffrischimpfung**	**weitere Auffrischimpfung**
Pneumokokken			
2 Mo. – 24 Mo.	Grundimmunisierung bzw. Nachholimpfungen gemäß Impfkalender STIKO		1 x PSV-23 (ab dem 6. LJ)
3 – 5 J.	1 x PCV-13*		1 x PSV-23* (nach 5 J.)
≥6 J. u. Erwachsene	1 x PCV-13*	PSV-23 (nach 2-6 Mo.)	1 x PSV-23 (nach 5 J.)**
* Patienten, die mit PSV vorgeimpft sind, erhalten 1 x PCV-13 in einem Mindestabstand von (1-) 5 Jahren ** Auffrischung bei Kindern < 10 J. schon nach 3 Jahren, spätere Wiederauffrischungen derzeit noch nicht definiert			
Meningokokken Serotyp A, C, W und Y			
2-11 Mo.	2 x Men-C (Abstand 2 Mo.)	Men-ACWY+ (nach 12 Mo.)	Men-ACWY (nach 6-12 Mo.)**
≥1 J. u. Erwachsene	1 x Men-ACWY+	Men-ACWY (nach 2 Mo.) +	Men-ACWY (alle 5 J.)
+ Zulassung beachten: Nimenrix®) ab vollendetem 12. Lebensmonat, Menveo® ab dem 2. Lebensjahr * spätere Auffrischungen mit MCV-ACWY alle 5 J.			
Meningokokken Serotyp B			
2-5 Mo.	3 x Men-B (Abstand 1 Mo.)	Men-B (nach 12 Mo.)	Notwendigkeit derzeit unklar
6-11 Mo.	2 x Men-B (Abstand 2 Mo.)	Men-B (2. LJ, Abstand 2 Mo.)	
12-23 Mo.	2 x Men-B (Abstand 2 Mo.)	Men-B (Abstand 12 Mo.)	
≥2 J. u. Erwachsene+	2 x Men-B (Abstand 1-2 Mo.)*	Notwendigkeit derzeit unklar	
+ für Erwachsene > 50 Jahre liegen keine Daten vor * bei 2 - 11-Jährigen Impfabstand mind. 2 Monate			
Haemophilus influenzae			
2 Mo.–5 J.	Grundimmunisierung gemäß Impfkalender STIKO		
> 5 Jahre	einmalige Impfung mit HiB-Konjugatimpfoff		
Influenza (Grippe)			
> 5 Jahre	jährliche Grippeschutzimpfung		

PCV-13	13-valenter Pneumokokken-Konjugatimpstoff	Prevenar-13®
PSV-23	23-valenter Pneumokokken-Polysaccharidimpfstoff	Pneumovax®
Men-C	Meningokokken-Konjugatimstoff Serotyp C	Meningitec®, NeisVac-C®, Menjugate®
Men-ACWY	Meningokokken-Konjugatimstoff Serotyp A, C, W, Y	Menveo®: Nimenrix®
Men-B	Quadrivalenter Meningokokkenimpfstoff Serotyp B	Bexsero®
HiB	*H. Influenzae* Typ B-Konjugatimpfstoff	ACT-Hib® (nur über Import)

SAPFIRE

Sepsis Associated Purpura Fulminans
International Registry – Europe

HOME | BACKGROUND | THE INTERNATIONAL SAPFIRE REGISTRY | JOIN THE REGISTRY | CONTACT | LOGIN

Welcome to SAPFIRE –
Europe's registry on sepsis-associated Purpura fulminans

http://www.sapfire-registry.org

SAPFIRE – Why a registry ?

„ Science tells us what we can do;
Guidelines what we should do;
Registries what we are actually doing. „

Lukas Kappenberger MD
Heart Rhythm Society Policy Conference
Washington DC 2005

SAPFIRE – Aims and Endpoints

Population	Patients diagnosed with sepsis-associated *Purpura fulminans* (excluding premature neonates)
Design	Prospective multi-center registry, based on systematic data acquisition
Aims	Collection and evaluation of data on sepsis-associated *Purpura fulminans* pertaining to • Incidence, course and causal pathogens • Disease management and outcomes • Biomarkers of disease progression and therapeutic efficacy
Endpoints	• All-cause in-hospital mortality • Morbidity scores at defined post-diagnosis intervals • Extent and severity of Purpura lesions and surgical interventions • Changes in hematological, coagulation and inflammatory biomarkers • Cumulative doses of blood products and anti-coagulants • Life support (mechanical ventilation, renal replacement therapy, vasopressor use) • Origin and causal pathogen of primary infection • Duration of hospitalization and ICU stay • Treatment-associated adverse events (bleeding, thrombosis)
Centers	Starting with 30 in Germany, Austria, Netherlands, Ireland, UK, Italy, Spain
Enrollment	Estimated approx. 50 patients/year

SAPFIRE – Responsibilities

Principal Investigator	Prof. Frank M. Brunkhorst, **MD** **Jena University Hospital** **Center for Clinical Studies** **Salvador-Allende-Platz 27, 07747 Jena** **Tel.: 03641-9-323381** **E-Mail: frank.brunkhorst@med.uni-jena.de**
Project management Biometry Data management	**Jena University Hospital** **Center for Clinical Studies**
Steering Committee	Jan Hazelzet, **MD, PhD, FCCM; *Erasmus Medical Center, Rotterdam*** Prof. Paul Knoebel, **MD; *Medical University of Vienna*** Simon Nadel, **MRCP; *St Mary's Hospital, Imperial College, London*** Michael Sasse, **MD; *Hannover Medical School*** Owen Smith, **MD; *Our Lady's Children's Hospital, Dublin***

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Thank you for your attention !

Jena Center for Clinical Studies

KKS Netzwerk
Koordinierungszentren für Klinische Studien

http://www.zks.uniklinikum-jena.de/

SAPFIRE – Why a registry ?

- Approach of choice in very rare diseases
- Real-world picture of disease presentation, treatment practices and outcomes
- Performance of treatment procedures and pharmaceuticals in heterogenous populations
- Comparative evaluation of non-standardized care procedures
- Opportunity for generalization of results toward a wide range of patients
- Possibility for post-hoc stratification of patient population
- Continuous information flow and feedback
- Valuable tool of performance benchmarking and quality assurance
- Transfer of innovative treatment strategies into the clinical routine

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Zentrum für Klinische Studien

Use of Electronic Health Records (EHRs) and Clinical Decision Support Systems (CDSSs) for Antimicrobial Stewardship

Use of Electronic Health Records and Clinical Decision Support Systems for Antimicrobial Stewardship

Table 1. Electronic Health Records and Clinical Decision Support Systems Currently Available in the United States

	EHRs		CDSSs				
Feature	Epic	Cerner	TheraDoc (Premier)	SafetySurveillor (Premier)	QC PathFinder (Vecna)	Sentri7 (Pharmacy OneSource)	MedMined (CareFusion)
EHR integration	NA	NA	Yes	No	Yes	Yes	No
Treatment guidelines	Order sets	Order sets	Yes	No	No	Yes (via embedded hyperlinks)	No
Real-time alerts	Yes	Yes (with IT customization)	Yes	Yes	Yes	Yes	Yes
Delayed alerts[a]	Yes	No	No	Yes	Yes	Yes	Yes
Customizable alerts	Yes	Yes (with IT customization)	Yes	Yes	Yes	Yes	Yes
Clinical information	Yes	Yes	Yes	Yes	No	Yes	Yes
Infection control software	Yes	No	Yes	Yes	Yes	Yes	Yes
Institutional antibiogram	Yes	No	Yes	Yes	Yes	Yes	Yes
Unit antibiogram	Yes	No	Yes	Yes	Yes	Yes (available in June 2014)	Yes
Prescriber metrics	Yes	No	Yes	Yes	No	No	Yes
Patient outcome tracking and reporting capabilities	No	No	No	No	No	No	No
Product cost	++++	++++	++++	+++	+++	+++	+++

Abbreviations: +++, >$100K; ++++, >$500K; CDSS, clinical decision support system; EHR, electronic health record; IT, information technology; NA, not applicable.

[a] With the delayed-alert feature, alerts do not occur in real time but 2–3 times a day, depending on how data from the hospital warehouse are uploaded to the server.

"There is now an urgent need for a new generation of EHRs and CDSSs that can provide ASPs with patient outcomes data and that can play a role in improving patient outcomes."

Clinical Infectious Diseases 2014;59(S3):S122–33

Antimicrobial Stewardship programs – costs and outcomes

Referenz	Bettenzahl	Einsparungen	AB-Resistenz und Infektionskontrolle
White et al. 1997	575	$803.910/Jahr	Reduzierte Resistenzraten für mehrere AB-Erreger
Bantar et al. 2003	250	$913.236/1,5 Jahre	Verm. Ceph3- u. Carbapenem-Verbrauch korr. M. verm. Resistenz
Carling et al. 2003	174	> $200.000/Jahr	Verm. Rate an nosokomialen C. diff. Infektionen u. Infektionen durch resistente Enterobacteriaceae
Montecalvo et al. 2001	650	$189.318/Jahr	Verm. Rate an Kolonisation mit VRE und BSI
Ozkurt et al. 2005	1200	$322.000/Jahr	Verm. Resistenzraten
Philmon et al. 2006	900	$1.841.203/ 3 Jahre	Verm. Resistenzraten gegenüber verschiedenen Antibiotika

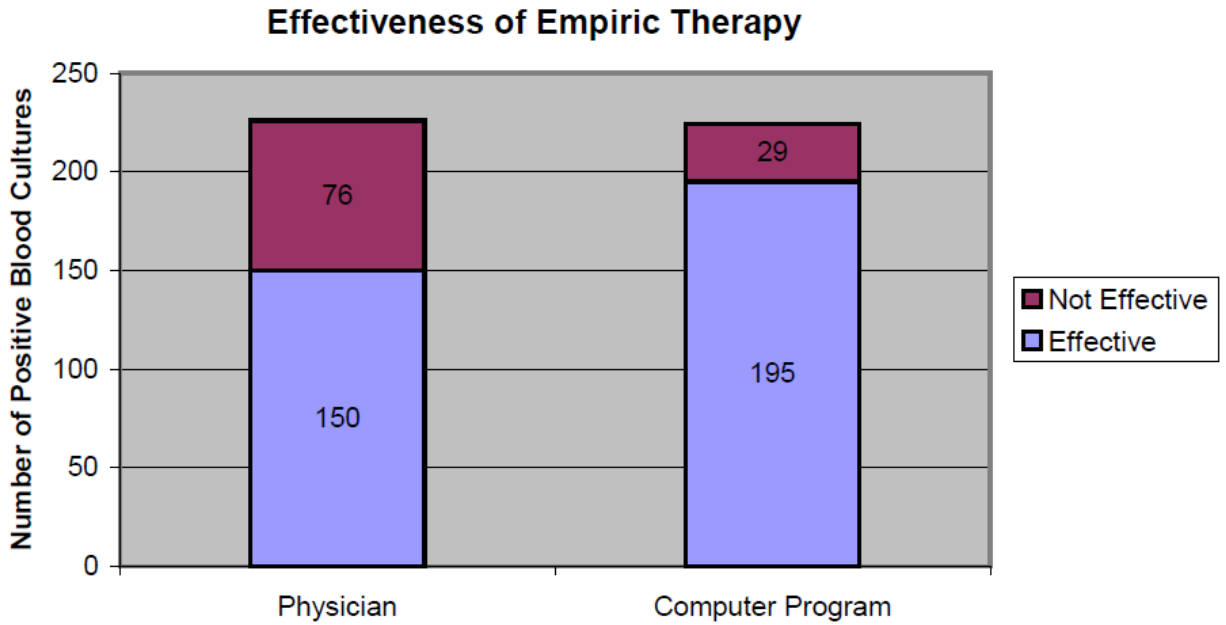
Hypothese: Haupteinspareffekt nicht über verringerten Antibiotikaverbrauch, sondern über geringere Resistenzraten.

nach Goff, Current Opinion in Infectious Diseases 2011, 24:S11-S20

Computerized antimicrobial decision support: an offline evaluation of a database-driven empiric antimicrobial guidance program in hospitalized patients with a bloodstream infection

International Journal of Medical Informatics

www.intl.elsevierhealth.com/journals/ijmi



International Journal of Medical Informatics (2004) 73, 455–460