Online Supplement to "High Early Mortality in Patients With *Staphylococcus aureus* Bloodstream Infection: A Call for Action"

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Appendix S1. Studies That Provided 2-Day, 3-Day, or 7-Day Mortality Data That Were Excluded From the Study of Early Mortality in Patients With *S. aureus* Bloodstream Infection

Reference	Study Design	Design Study Period; Country; No. of Centers	SABI Type	Study Objective(s)	All-Cause Mortality				Reason for Exclusion
Romero-Vivas 1995[42]	Prospective	Jan 1990–Sept 1993 Spain 1 university hospital	MSSA, MRSA	To compare the clinical characteristics and mortality of nosocomial MSSA and MRSA BI		**MSSA (N=100)**	**MRSA (N=84)**	**Overall (N=184)**	This study was done during an outbreak of MRSA infection at the facility.
					2-d	10%	20%	15%	
Collignon 2005[43]	Retrospective	1999–2002 Australia 17 hospitals	MSSA, MRSA	To estimate the incidence of SABI in Australia	I hospital 7-day mortality: 27/267 (10%)				Only 7-day mortality data for 1 of 17 hospitals
Liao 2005[44]	Prospective June 2001–May 2002 Taiwan 1 hospital	MSSA, MRSA	93 with CO SABI MSSA 69%; MRSA 31%	To compare the clinical characteristics and prevalence of MRSA infection in CO vs CO-HCA SABI		**Overall**	**CO**	**CO-HCA**	<100 cases (N=93)
					3-d	3.20%	5.40%	1.80%	
					7-d	9%	10.80%	7%	
					Hosp	18.30%	13.50%	12.90%	
*Hanses 2010[45]	Retrospective	Jan 2004–June 2005 Germany 1 hospital	MSSA, MRSA	To evaluate risk factors associated with long-term survival in patients with SABI	3-d	2/80 (2.5%)			<100 cases (N=80)
					7-d	6/80 (7.5%)			
					30-d	23/80 (29%)			
Lee 2013[46]	Prospective	Jan–Oct 2010 Taiwan 1 teach hospital	CO- and CO-HCA MRSA	To compare the clinical features and mortality of CO and CO-HCA MRSA BSI		**CO (N=48)**	**CO-HCA (N=13)**		<100 cases (N=51)
					7-d	0	7 (15%)		
					30-d	1 (8%)	14 (29&)		
Kaku 2014[47]	Retrospective	2008–2011 Japan 1 teaching hospital	MRSA	To assess the clinical characteristics of MRSA BI	7-d	12%			<100 cases (N=83)
					30-d	18%			
Bouiller 2016[48]	Retrospective	2010–2014 France 1 university hospital	MSSA	To compare the outcome of SABI caused by CC398 strains vs non-CC398 strains		**CC398 (N=67)**	**Non-CC398 (N=134)**		Case/control study
					7-d	24%	17%		
					30-d	42%	28%		
Jayaweera 2017[49]	Retrospective	Mar 2012–Dec 2013	MRSA	To evaluate the outcome of vancomycin treatment of MRSA BSI	7-d	15/61 (24.6%)			<100 cases (N=61)
Hos 2017[50]	Prospective	Jan 2006–Dec 2012 Germany 1 hospital	MRSA	To examine the association between vancomycin MIC and outcome of MRSA BI	3-d	5/91 (5.5%)			<100 cases (N=91)
					30-d	29/91 (32%)			
Miller 2018[51]	Prospective	2011–2014 Argentina 3 hospitals	MSSA	To evaluate the impact of the cefazolin inoculum effect on outcome of MSSA BI		**CzIE (N=35)**	**No CzIE (N=42)**		<100 cases (N=77)
					7-d	5 (12%)	2 (6%)		
					30-d	15 (40%)	5 (15%)		

Reference	Study Design	Design Study Period; Country; No. of Centers	SABI Type	Study Objective(s)	All-Cause Mortality				Reason for Exclusion
Henderson 2019[52]	Retrospective	Jan 2007–Sept 2013 Australia and New Zealand 27 hospitals and labs	MSSA	To compare the outcome of pcn-susceptible MSSA BSI treated with pcn or flucloxacillin		**Pcn (N=315)**	**Flucloxacillin (N=600)**		915 cases studied of 1,394 with pcn-susceptible MSSA BI; subset of 13,107 episodes of SABI
					7-d	5 (2%)	41 (6%)		
					30-d	33 (10%)	85 (14%)		
Grillo 2019[53]	Retrospective	2011–2017 Spain 1 university hospital	MSSA	To compare a beta-lactam plus daptomycin and beta-lactam only on outcome of MSSA BI		**BL + Dapto (N=136)**	**BL only (N=214)**		Only 350 of 514 cases of MSSA BI met inclusion criteria
					7-d	12 (9%)	15 (7%)		
					30-d	26 (19%)	34 (16%)		
Talon 2002[54]	Prospective	Jan 1997–Dec 1998 France 1 hospital	MSSA, MRSA	To compare clinical characteristics and mortality of patients with MSSA and MRSA BI	2-d	9/99 (9%)			<100 cases (N=99); only reported attributable mortality
					7-d	20/99 (20%)			
					14-d	27/99 (27%)			
Paul 2010[55]	Retrospective	1988–1994 1999–2007 Israel 1 hospital	MSSA	To compare the outcome of MSSA BI treated with different beta-lactam antibiotics	2-d	52/541 (9.6%)			736 episodes of MSSA BI; only patients with MSSA BI treated with a beta-lactam antibiotic (N=541) included in the study
					30-d	202/541 (37.3%)			
Bader 2006[56]	Retrospective	Jan 2003–Dec 2004 United States 2 hospitals	MSSA, MRSA	To determine predictors of mortality in patients age >60 with SABI		**MSSA (N=58)**	**MSSA (N=74)**	**Overall (N=132)**	Only patients age ≥60 with SABI included
					7-d	3 (5%)	12 (20%)	18 (14%)	
Liao 2008[57]	Prospective	Jan 2001–May 2002 S. Korea 1 hospital	MRSA	To determine risk factors for mortality in patients presenting to ED with MRSA BI	3-d	24/177 (13.6%)			Included polymicrobial cases
					7-d	28/177 (15.8%)			
					14-d	37/177 (21%)			
*Ponce de Leon 2010[58]	Retrospective	Jan 2003–Dec 2007 Mexico 1 hospital	MSSA, MRSA	To define the epidemiology of SABI at a tertiary care hospital in Mexico City		**MSSA (N=93)**	**MSSA (N=79)**	**Overall (N=172)**	Included polymicrobial cases
					7-d	13 (14%)	5 (6%)	18 (10.5%)	
					30-d	20 (22%)	17 (22%)	37 (22%)	
Paulsen 2015[59]	Retrospective	1996–2011 Norway 2 hospitals	MSSA, MRSA	To describe the epidemiology of SABI in one county in Norway	7-d	54/373 (14.5%)			Included polymicrobial cases
					30-d	102/373 (27.3%)			
You 2017[60]	Retrospective	2010–2012 Hong Kong 26 hospitals	MRSA	To identify clinical characteristics and predictors of mortality related to MRSA BI	7-d	112/1,133 (10%)			Included polymicrobial cases
					30-d	367/1,133 (32.4%)			
Ben-Zvi 2019[61]	Retrospective Uncontrolled before and after study	Jan 2015–May 2016 (before) Jan 2016–Aug 2017 (after) Israel 1 hospital	MSSA, MRSA	Influence of GeneXpert MRSA/SA testing on outcome of SABI		**Before (N=125)**	**After (N=129)**		Excluded patients in ICU and those who died on same day blood cultures were done
					7-d total	17%	16%		
					7-d MSSA	14%	16%		
					7-d MRSA	21%	19%		
Tissot 2014[62]	Retrospective	2001–2010 Switzerland 1 university hospital	MRSA	To assess the impact of infectious diseases consultation (IDC) on management of MRSA BI		**IDC (N=124)**	**No IDC (N=32)**	**Overall (N=156)**	12 cases excluded because they died before blood culture results were available
					7-d total	6 (5%)	7 (22%)	13 (8.3%)	
					(Risk factors for 7-d mortality: pneumonia, severity of infection, no IDC, and no removal of infectious focus; CIs were wide)				

Reference	Study Design	Design Study Period; Country; No. of Centers	SABI Type	Study Objective(s)	All-Cause Mortality				Reason for Exclusion
*Robinson 2012[63]	Retrospective	June 1997–June 2007 Australia 1 hospital	MSSA, MRSA	To determine the impact of formal infectious diseases consultation (IDC) on mortality of SABI		**IDC (N=162)**	**No IDC (N=437)**		Study population was all MRSA BSI and a 20% random sample of all MSSA BSI
					7-d total	3%	16.5%		
					30-d	8%	27%		
Seas 2018[64]	Prospective	Jan 2011–July 2014 Latin America 24 hospitals in 9 countries	MSSA, MRSA	To assess the clinical impact of SABI in Latin America	7-d	48/915 (5.2%)			Only evaluated attributable mortality
Chen 2015[65]	Retrospective	2002–2011 Taiwan 1 university hospital	MSSA	To compare the clinical features and molecular typing of MSSA causing CO- and HO BSI		**CO-HCA (N=162)**	**CO (N=32)**	**HO (N=91)**	Study population was a random sample of patients with MSSA BSI
					7-d	12 (7.4%)	3 (9.4%)	11 (12.1%)	
					Overall 7-d		26/285 (9.1%)		
*Kim 2019[66]	Prospective	2016–2017 6 hospitals South Korea	MSSA, MRSA	To evaluate impact of risk factors for SABI	7-d	45/567 (8%)			Included polymicrobial cases
					14-d	65/567 (11.5%)			
					28-d	85/567 (25%)			
*Seifert 2008[67]	Prospective	2006–2007 Germany	MSSA, MRSA	To evaluate the epidemiology and prognosis of SABI in Germany	7-d	21/263 (8%)			Only available in German
					In-hospital	58/263 (22%)			
*Turnidge 2007[68]	Prospective	2005–2006 Australia	MSSA, MRSA	To provide preliminary data on the outcome of SABI in Australia	7-d	86/768 (11.2%)			Of 1,511 cases of SABI, outcome data on only 51%

MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*; BI=bloodstream infection; SABI=*S. aureus* bloodstream infection; CO=community-onset; HO=hospital-onset; COHCA=community-onset, healthcare-associated; MIC=minimal inhibitory concentration; CzIE=cefazolin inoculum effect; pcn=penicillin; BL=betalactam; Dapto=daptomycin; CIs=confidence intervals

*This study was included in the meta-analysis of 7-day mortality by Bai et al. (reference 1 in the article). However, this study did not meet inclusion criteria for the present study for the reason noted in the table.

Appendix S2. Studies of SABI That Reported Mortality Rates ≤2 or ≤3 days After the First Positive Blood Culture (**Table S1** Below)

Five studies reported 2-day mortality rates for SABI.[69-73] Two studies of MRSA BI identified risk factors for 2-day mortality using multivariate analysis.[74-76] Although the 2-day mortality rates were similar (8.5% and 6.5%) in these two studies, there were considerable differences in the characteristics of the study populations (**Table S2** below). In a comparison of the results of the multivariable analysis in these two studies, there was no overlap in the significant risk factors for 2-day mortality (**Table S3** below). In both multivariate models the 95% confidence intervals of the odds ratio were wide for all the significant variables due to the small number of deaths at two days that limits interpretation of the findings. However, these studies illustrate how differences in the characteristics of a study population of patients with SABI affect the factors associated with mortality. Three studies were identified that reported 3-day mortality rates for SABI (**Table S1** below), but there was no evaluation of risk factors for 3-day mortality.[74-76]

Table S1. Studies of *S. aureus* Bloodstream Infection Published Since 2000 That Reported 2-day and 3-day Mortality Rates

Reference	Design; Study Period; Country; No. of Hospitals	SABI Type	Study Population	Study Objective(s)	All-Cause Mortality at Specified Days After Day of 1st Positive Blood Culture	Of All Patients Who Died, % Dying ≤2 Days or ≤3 Days
Studies reporting 2-day mortality rates						
Perovic 2006[69]	Prospective Nov 99–Oct 2002 South Africa 2 hospitals	MSSA, MRSA	N=449 CO 45% HO 55% MSSA 344 MRSA 105	To determine mortality rate of SABI and risk factors for 14-day mortality	2-d 21/449 (4.7%) 14-d 104/449 (23.2%)	21/104 (20%)
Stevens 2012[70]	Published data[a] Jan 2007–June 2009 United States 2 hospitals	MRSA	N=200 (all HO)	To compare a severity of illness score in ICU and non-ICU patients with MRSA BI	**ICU N=76** / **Non-ICU N=124** / **Overall N=200** 2-d 4 (5%) / 5 (4%) / 9 (4.5%) 7-d 12 (16%) / 14 (11%) / 26 (13%) 14-d 15 (20%) / 17 (14%) / 32 (16%) 30-d 19 (25%) / 19 (16%) / 38 (19%)	ICU 4/19 (21%) Non-ICU 5/19 (26%) Overall 9/38 (24%)
Gasch 2013[71]	Prospective Jun 2008–Dec 2009 Spain 21 hospitals	MRSA	N=579 CO (238) HO (338)	To identify predictive factors of early (2-day) mortality in patients with MRSA BI	2-d 49/579 (8.5%) 30-d 179/579 (31%)	49/179 (27%)
Cuervo 2016[72]	Prospective Jun 2008–Dec 2009 Spain 21 hospitals (same data as Gasch 2013)	MRSA	N=579 (same study population as Gasch et al.74)	To compare the treatment and outcome of patients age ≥75 vs age <75 with MRSA BI	**Age ≥75 N=231** / **Age <75 N=348** / **Overall N=579** 2-d 28 (12%) / 21 (6%) / 49 (8.5%) 30-d 99 (43%) / 80 (23%) / 179 (31%)	Age ≥75 28/99 (28%) Age <75 21/80 (26%) Overall 49/179 (27%)
Kim 2019[73]	Prospective Aug 2008–June 2011 S. Korea 1 hospital	MRSA	N=385 HO 75% CO-HCA 21% CO 4%	To identify clinical and microbiologic factors associated with early (2-day) mortality	2-d 25/385 (6.5%) 28-d 50/385 (13%)	25/50 (50%)
Studies reporting 3-day mortality rates						
Thwaites 2010[74]	Prospective Nov 2008–Nov 2009 UK – 8 hospitals Vietnam – 3 hospitals Nepal – 1 hospital	MSSA, MRSA	N=587 CO and HO; MRSA 21%	To assess and compare management and adherence of treatment guidelines for SABI in 3 countries	(All-cause mortality is for all countries combined) 3-d 45/587 (7.7%) 14-d 100/587 (17%)	45/100 (45%)
Forsblom 2013[75]	Retrospective 2000–2002 2006–2007 Finland 1 hospital	MSSA	N=342 CO 43% CO-HCA 57%	To compare the outcome of SABI with informal or formal ID consultation compared to no consultation	**Informal/Formal (N=307)** / **None (N=35)** / **Overall (N=342)** 3-d 2 (0.6%) / 9 (26%) / 11 (3.2%) 7-d 7 (2.3%) / 9 (26%) / 16 (4.7%) 28-d 22 (7%) / 12 (34%) / 34 (10%)	Informal/formal 2/22 (9%) None 9/12 (75%) Overall 11/34 (32%)
Nambiar 2018[76]	Prospective Jan 2013–Apr 2015 Multinational 11 hospitals	MSSA, MRSA	N=1,851 CO, CO-HCA, and HO	To determine if mortality is a valid and feasible quality of care outcome measure for SABI	3-d 132/1,851 (7%) 7-d 207/1,851 (11.2%) 30-d 410/1,851 (22.3%) 3-day mortality ranged from 4%–14% in 11 hospitals (p=0.03)	132/410 (32%)

MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*; BI=bloodstream infection; SABI=*S. aureus* bloodstream infection; CO=community-onset; HO=hospital-onset; CO-HCA=community-onset, healthcare-associated; ICU=intensive care unit; ED=Emergency department; hosp=hospital; ID=infectious diseases; UK=United Kingdom

[a]Butterfield JM, Tsuji BT, Brown J, et al. Predictors of Agr Dysfunction in Methicillin-Resistant Staphylococcus aureus (MRSA) Isolates Among Patients With MRSA Bloodstream Infections. *Antimicrob Agents Chemother*. 2011;55:5433-5377.

Table S2. Characteristics of the Study Populations in Two Studies That Evaluated Risk Factors for 2-Day Mortality After the First Positive Blood Cultures in Patients With *S. aureus* Bloodstream Infection

Characteristic	Gasch[71]	Kim[73]
No. of episodes of 2-day mortality/ Total no. of cases	48/579 (8.5%)[a]	25/385 (6.5%)[a]
Acquisition of BI:		
Community-onset	58%	4%
CO-HCA	-	21%
Hospital-onset	42%	75%
Severe sepsis/shock	NS	80%
Source of BI:		
Respiratory	27%	20%
Unknown	35%	32%
IVC	14%	36%
Underlying disease		
Cancer	NS	60%
Cirrhosis	NS	32%

[a]Chi-square=1.0665; *p*=0.30
CO-HCA= community-onset, healthcare-associated; NS=not stated; IVC=intravascular catheter

Table S3. Comparison of the Multivariate Analysis in Two Studies to Identify Risk Factors for Mortality ≤2 Days After the First Positive Blood Cultures in Patients With *S. aureus* Bloodstream Infection

Risk Factor	Gasch[71]	Kim[73]
Rapidly fatal underlying disease	3.67 (1.32–10.24)	NS
LRT source	3.76 (1.31–10.83)	NE
Unknown source	2.83 (1.11–7.21)	NE
Healthcare- or community-associated infection	2.59 (1.16–5.77)	NE
Pitt bacteremia score >3	3.99 (1.72–9.24)	NE
Inappropriate empiric antibiotic therapy	3.59 (1.63–7.89)	NS
Liver cirrhosis	NE	3.79 (1.38–10.37)
Severe sepsis or septic shock	NE	10.98 (3.82–31.52)

NE=not evaluated; LRT=lower respiratory tract infection; NS=not significant

Appendix S3. Studies of *S. aureus* Bloodstream Infection Published Since 2000 That Reported 7-Day All-Cause Mortality After the First Positive Blood Culture

Reference	Design; Study Period; Country; No. of Hospitals	SABI Type	Study Population (No. of Episodes; Acquisition of SABI)	Study Objective(s)	All-Cause Mortality at Specified Days After Day of 1st Positive Blood Culture	Of All Patients Who Died in Hospital, % Dying ≤7 Days
Cordova 2004[7]	Retrospective 1997–1999 Australia 5 hospitals	MSSA MRSA	501 (CO, CO-HCA, HO)	To define the epidemiology of MRSA BI	**MRSA (N=55)** / **MSSA (N=446)** / **Overall (N=501)** 7-d: 9 (16%) / 38 (8.5%) / 47 (9.4%) Hosp: 15 (27%) / 75 (17%) / 90 (18%) 7-d mortality MRSA vs MSSA, p=0.06	**Overall** 47/90 (52%) **MSSA** 38/75 (51%) **MRSA** 9/15 (60%)
Lyytikainen 2005[8]	Retrospective[a] 1995–2001 Finland All hospitals	MSSA	4,749 (CO and HO)	To identify trends in incidence and outcome of SABI	**CO (N=2,546)** / **HO (N=2,203)** / **Overall (N=4,749)** 7-d: 178 (7%) / 264 (12%) / 442 (9%0 28-d: 331 (13%) / 485 (22%) / 816 (17%) 7-d mortality CO vs HO, p<0.001	**Overall** 442/816 (54%) **CO** 178/331 (54%) **HO** 264/485 (54%)
Wang 2008[9]	Prospective Jan 2001–Dec 2006 Taiwan 1 hospital	MSSA MRSA	215 MSSA MRSA (CO; excluded CO-HCA BI)	To compare the outcome of patients with CO MRSA and MSSA BI	**MSSA (N=185)** / **MRSA (N=30)** / **Overall (N=215)** 7-d: 16 (8.7%) / 1 (3.3%) / 17 (8%) 30-d: 24 (13%) / 3 (10%) / 27 (12.5%) 7-d mortality, MSSA vs MRSA, p=0.32	**Overall** 17/27 (63%) **MSSA** 16/24 (67%) **MRSA** 1/3 (33%)
Kim 2020[10]	Retrospective Mar 2014–Dec 2018 Korea 1 hospital	MSSA MRSA	278 (CO, CO-HCA)	To define the characteristics and all-cause mortality of SABI; and risk factors for mortality in CKD with and without dialysis	**ND-CKD (N=43)** / **Daily (N=58)** / **Non-CKD (N=177)** / **Overall (N=278)** 7-d: 26% / 12& / 8% / 12% 30-d: 40% / 28% / 12% / 26%	**Overall** 33/72 (46%)
Turnidge 2009[11]	Prospective June 2007–May 2008 Australia and New Zealand 27 hospitals	MSSA MRSA	1,994 (CO and HO)	To determine risk factors for mortality for SABI	7-d: 215/1,194 (10.8%) 30-d: 384/1,865 (20.6%)	**Overall** 215/384 (56%)
Kempker 2010[12]	Retrospective 2005–2008 United States Population-based study in counties around Atlanta	MRSA	1,104 (CO, CO-HCA, HO) 1,104 (CO, CO-HCA, HO)	To evaluate the association of USA300 genotype with increased mortality in patients with MRSA BSI	4,344 cases of MRSA BSI; 1,104 genotyped; 414 (38%) USA300 **USA300 (N=414)** / **Non-USA300 (N=690)** / **Overall (N=1,104)** (%) 7-d: 50 (12) / 67 (9.7) / 117 (10.6) in-hosp: 68 (16) / 136 (20) / 204 (18.5) 7-d mortality USA300 vs non-USA300: p=0.216	**Overall** 117/204 (57%) **USA300** 50/68 (74%) **Non-USA300** 67/136 (49%) p<0.01 vs USA300
Kok 2011[13]	Retrospective Aug 2008–Feb 2010 Australia 1 hospital	MSSA MRSA	187 (CO, CO-HCA, HO) 187 (CO, CO-HCA, HO)	To evaluate the epidemiology of SABI and to identify factors, if prevented, would reduce the occurrence of HCA SABI	**MSSA (N=112)** / **MRSA (N=75)** / **Overall (N=187)** 7-d: 10 (8.9%) / 11 (14.7%) / 21 (10.7%) 30-d: 19 (17%) / 20 (26.7) / 39 (20.9%) 7-d mortality MSSA vs MRSA, p=0.22	**Overall** 21/39 (54%) **MSSA** 10/19(53%) **MRSA** 11/20 (55%)

Reference	Design; Study Period; Country; No. of Hospitals	SABI Type	Study Population (No. of Episodes; Acquisition of SABI)	Study Objective(s)	All-Cause Mortality at Specified Days After Day of 1st Positive Blood Culture	Of All Patients Who Died in Hospital, % Dying ≤7 Days
Lamagni 2011[14]	Retrospective 2004–2005 England Population-based study	MRSA	9,001 (Not stated)	To determine the 30-day mortality risk related to MRSA BSI	7-d 1,825/9,001 (20%) 30-d 3,450/9,001 (38%)	**Overall** 1,825/3,450 (53%)
Tong 2012[15]	Prospective 2007–2010 Australia/NZ 24 hospitals	MSSA MRSA	7,539 (CO, CO-HCA, HO)	To determine the impact of ethnicity and socioeconomic status on the incidence and outcome of SABI	7-d 692/7,539(9.2%) 30-d 1,256/7,539 (16.7%)	**Overall** 692/1,256 (55%)
Stevens 2012[4]	Retrospective Jan 2007–June 2009 United States 2 hospitals Analysis of previously published data	MRSA	200 (Not stated)	To compare a severity of illness score in ICU and non-ICU patients with MRSA BI	**ICU N=76** / **Non-ICU N=124** / **Overall N=200** 2-d 4 (5%) / 5 (4%) / 9 (4.5%) 7-d 12 (16%) / 14 (11%) / 26 (13%) 14-d 15 (20%) / 17 (14%) / 32 (16%) 30-d 19 (25%) / 19 (16%) / 38 (19%)	**Overall** 26/38 (68%)
Forsblom 2013[5]	Retrospective 2000–2002 2006–2007 Finland 1 hospital	MSSA	342 (CO, CO-HCA, HO)	To compare the outcome of SABI with informal IDC compared to formal consultation or no consultation	**Informal/Formal (N=307)** / **None (N=35)** / **Overall (N=342)** 3-d 2 (0.6%) / 9 (26%) / 11 (3.2%) 7-d 7 (2.3%) / 9 (26%) / 16 (4.7%) 28-d 22 (7%) / 12 (34%) / 34 (10%)	**Overall** 16/34 (47%)
Ong 2013[16]	Retrospective Jan 1998–Dec 2007 Australia 1 hospital	MSSA (N=363) MRSA (N=76)	439 (CO, CO-HCA, HO)	To determine long-term survival of patients with SABI	7-d 42/439(9.6%) 30-d 75/439 (17%)	**Overall** 42/75 (56%)
Melzer 2013[17]	Prospective Aug 2007–Jul 2011 England 2 university hospitals	MSSA	403 (CO and HO)	To determine the outcome of CO and HO MSSA BI	**CO (N=256)** / **HO (N=147)** / **Overall (N=403)** 7-d 41 (16%) / 3 (2%) / 44 (11%) 30-d 71 (28%) / 31 (21%) / 101 (26%) 7-d mortality CO vs HO, $p<0.001$	**Overall** 44/101 (44%) **CO** 41/71 (58%) **HO** 3/31 (9.7%) $p<0.001$ vs CO
Bassetti 2017[18]	Retrospective 2010–2014 Italy 2 university hospitals	MSSA MRSA	337 (CO, CO-HCA, HO)	To evaluate the characteristics of SABI and risk factors for 7- and 30-day mortality	**MSSA (N=205)** / **MRSA (N=132)** / **Overall (N=337)** 7-d 14 (6.8%) / 30 (22.7%) / 44 (13%) 30-d 39 (19%) / 47 (38%) / 86 (25.5%) 7-d mortality MSSA vs MRSA, $p<0.001$	**Overall** 44/86 (51%) **MSSA** 14/39 (36%) **MRSA** 30/47 (64%) $p<0.01$ vs MSSA
Bassetti 2018[19]	Retrospective 2011–2014 Italy 2 hospitals	MSSA MRSA	332 (CO, CO-HCA, HO)	To identify risk factors for early and late mortality of SABI in patients age ≥75	**<75 (N=219)** / **≥75 (N=118)** / **Overall (N=332)** 7-d 20 (9.2%) / 24 (20.3%) / 44 (13%) 30-d 45 (21%) / 41 (36%) / 86 (26%) 7-d and 30-d all-cause mortality was significantly greater in patients age ≥75	**Overall** 44/86(51%) **≤75** 20/45 (45%) **≥75** 24/41 (59%) $p=0.19$ vs <75

Reference	Design; Study Period; Country; No. of Hospitals	SABI Type	Study Population (No. of Episodes; Acquisition of SABI)	Study Objective(s)	All-Cause Mortality at Specified Days After Day of 1st Positive Blood Culture	Of All Patients Who Died in Hospital, % Dying ≤7 Days
Davis 2018[20]	Retrospective[b] Jan 2007–Sept 2013 Australia/NZ 24 hospitals	MSSA	7,321 (type not stated due to missing data)	To compare the outcome of MSSA BI treated with flucloxacillin or cefazolin	**Flucloxacillin (N=6,529)** / **Cefazolin (N=792)** 7-d: 294 (4.5%) / 29 (3.7%) 30-d: 731 (11.2%) / 83 (10.5%)	**Overall** 323/814 (39.7%) **7-d Fluclox** 294/731 (40%) **7-d Cefaz** 29/83 (35%)
Nambiar 2018[6]	Prospective Jan 2013–Apr 2015 Multinational 11 hospitals	MSSA MRSA	N=1,851 (CO, CO-HCA, and HO)	To determine if mortality is a valid and feasible quality of care outcome measure for SABI	3-d: 132/1,851(7%) 7-d: 207/1,851 (11.2%) 30-d: 410/1,841 (22.3%) 7-day mortality ranged from 8%–20% in 11 hospitals (p=0.003)	207/410 (50.5%)
Kang 2019[21]	Prospective Jan 2009–Feb 2018 Korea 14 hospitals	MSSA MRSA	1,917 (CO, CO-HCA, HO)	To compare duration of SABI based on methicillin resistance and focus of infection	All cause 7-d mortality: Enrolled: N=1,917: 159 (8.3%) Excluded: N=695[c]: 162 (23.3%) Enrolled+ Excluded: N=2,612: 321 (12.3%) In-hospital mortality of Enrolled + excluded: 658/2,612 (25.2%)	321/658 (48.7%)
Kim 2019[22]	Prospective[d] 1 hosp Jan 2009–Oct 2016 10 hospitals Sept 2013–Jan 2017 S. Korea	MSSA (N=1045) MRSA (N=1053)	2,098 (CO, CO-HCA, HO)	To compare outcome of SABI according to treatment duration with or without factors necessitating longer treatment	7-d: 282/2,098 (13.4%) 14-d: 376/2,098 (17.9%) 30-d: 465/2,098 (22.2%)	282/465 (61%)
Zheng 2020[23]	Retrospective 2013–2018 China 1 university hospital	MSSA (N=103) MRSA (N=192)	295 with monomicrobial BI (CO and HO)	To identify clinical findings and risk factors for polymicrobial SABI vs monomicrobial SABI[e]	**Mono (N=295)** / **Poly (N=54)** / **Overall (N=349)** 7-d: 22 (7.5%) / 9 (17%) / 31 (9%) 14-d: 33 (11%) / 13 (24%) / 46 (14%) 28-d: 45 (15%) / 16 (30%) / 61 (18%)	22/45 (49%)
Green 2020[24]	Prospective Pre-intervention: 2009–2013 Post-intervention: Jan 2014–June 2015 New Zealand 1 hospital	MSSA MRSA	598 (CO, CO-HCA, HO)	To evaluate a care bundle for managing SABI on outcome (pre-post intervention study)[f]	**Pre (N=447)** / **Post (N=151)** / **Overall (N=598)** 7-d: 51 (11.4%) / 16 (10.6%) / 67 (11%) 14-d: 60 (13.4%) / 22 (14.6%) / 82 (13.7%) 30-d: 83 (18.6%) / 31 (20.5%) / 114 (19%) 7-day mortality Pre vs Post, p=0.78	**Overall** 67/114 (59%) **Pre** 51/83 (61%) **Post** 16/31 (52%) p=0.34 vs Pre

Reference	Design; Study Period; Country; No. of Hospitals	SABI Type	Study Population (No. of Episodes; Acquisition of SABI)	Study Objective(s)	All-Cause Mortality at Specified Days After Day of 1st Positive Blood Culture				Of All Patients Who Died in Hospital, % Dying ≤7 Days
Lee 2021[25]	Retrospective June 2014–June 2019 Korea 1 hospital	MSSA	244 (CO, HO)	To evaluate the association between *agr* dysfunction and mortality in patients with MSSA BI		**Func *agr* (N=153)**	**Dysfunc *agr* (N=591**	**Overall (N=244)**	**Overall** 18/36 (50%) **Func *agr*** 10/22 (45%) **Dysfunc *agr*** 8/14 (57%) *p*=0.49 vs Func *agr*
					7-d	10 (6.5%)	8 (8.8%)	18 (7.4%)	
					30-d	22 (14.4%)	14 (15.4%)	36 (14.8%)	
					7-d Func *agr* vs Dysfunc *agr*, *p*=0.36				
Kaasch 2014[26]	Retrospective review of 5 prospective studies 2006–2011 20 hospitals in 5 countries: 2 Germany 2 Spain 15 UK 1 US	MSSA MRSA	3,395	To describe variation in clinical presentation of SAB between study populations and to identify common determinants of outcomes		**Pooled Mortality**	**Mortality Range[g]**	**p value[h]**	**Overall (by 30 days)** 317/711 (44.6%)
					7-d	317 (9.4%)	7.3%–12.5%	0.03	
					14-d	492 (14.6%)	11.2%–20.4%	0.002	
					30-d	711 (21.2%)	18.3%–29.4%	0.04	

MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*; BI=bloodstream infection; SABI=*S. aureus* bloodstream infection; CO=community-onset; HO=hospital-onset; CO-HCA=community-onset, healthcare-associated; ND-CKD=non-dialysis chronic kidney disease; CKD=chronic kidney disease; ED=emergency department; IDC=infectious diseases consultation; Mono=monomicrobial; Poly=polymicrobial; Pre=pre-intervention; Post=post-intervention; Func *agr*=functional accessory gene regulator; Dysfunc *agr*=dysfunctional accessory gene regulator; UK=United Kingdom; US=United States

[a]Population-based study of SABI in Finland. The authors noted that in Finland methicillin-susceptible *S. aureus* (MSSA) causes more than 99% of all SABI. Therefore, this study was considered to include only MSSA bloodstream infections.

[b]This study utilized a subset of the full ANZCOSS (Australian New Zealand Cooperative on Outcomes in Staphylococcal Sepsis) dataset that included only those patients with MSSA bloodstream infection whose definitive treatment was either flucloxacillin or cefazolin; although this study focused on specific treatment regimens for SABI, the study populations were large and, therefore, it was included in this review.

[c]This study focused on duration of SABI. There were 695 episodes in which duration of BI could not be determined, and these cases were excluded. However, the authors reported findings in these 695 episodes in supplemental data and reported that 162 deaths occurred within seven days of the first positive blood culture in the 695 excluded episodes. It was also reported that some of the patient characteristics of the 695 episodes were significantly different from 1,917 episodes included in the study. The results of seven-day mortality are reported for 695 episodes that were excluded along with the results for 1,917 episodes with known duration of BI.

[d]444 episodes of SABI were excluded from the study because patients declined participation; in the early part of this study informed consent was required, but this requirement was waived later in the study period. The characteristics of the 444 who did not sign consent were not provided in supplemental data. However, because the study population was large (N=2,098) it was included in this review.

[e]Although this study included polymicrobial BI, it was included in this review because the findings in the monomicrobial episodes were reported separately.

[f]There were only eight episodes of MRSA bloodstream infection. There was no significant difference in seven-day, 14-day, or 30-day mortality rates before or after the intervention.

[g]Range of mortality rate for five studies.

[h]p value for comparison of mortality rates of five studies.

Appendix S4. Bloodstream Infection Mortality Risk Score (BSIMRS)[a]

Variable	Points
Malignancy	3
Liver cirrhosis	4
Source of infection not urinary tract or central venous catheter	4
Pitt bacteremia score	
0–1	0
2–3	2
≥4	5

[a]Al-Hasan MN, Lahr BD, Eckel-Passow JE, Baddour LM. Predictive Scoring Model of Mortality in Gram-Negative Bloodstream Infection. *Clin Microbiol Infect*. 2013;19:948–954.

Appendix S5. Pitt Bacteremia Score (PBS)[a,b]

Criterion	Points
Fever (oral temperature)	
≤35°C or ≥40°C	2
35.1–36.0°C or 39.0–39.9°C	1
36.1–38.9°C	0
Hypotension Acute hypotensive event with drop in systolic blood pressure ≥30 mm Hg and diastolic blood pressure ≥20 mm Hg or Requirement for intravenous vasopressor agents or Systolic blood pressure ≤90 mm Hg	2
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Alert	0
Disoriented	1
Stuporous	2
Comatose	4

[a]All criteria are graded within 48 hours before or on the day of first positive blood culture. The highest point score during that time is recorded.

[b]Paterson DL, Ko WC, Von Gottberg A, et al. International Prospective Study of *Klebsiella* pneumoniae bacteremia: Implications of Extended-Spectrum b-lactamase Production in Nosocomial Infections. *Ann Intern Med*. 2004;140: 26–32.

Appendix S6. Significant Independent Variables in the Emergency Department Bacteremia Mortality Model (ED-BM)[a]

Age, years
  <65
  65–84
  ≥85

Ear temperature, °C
  36.1–38.9
  35.1–36.0 or 39.0–39.9

Hypotension
Mechanical ventilation

Mental status
  Alert (GCS 15)
  Disoriented (GCS 9–14)
  Stuporous (GCS 4–8)

Cancer
Liver cirrhosis
Infection source   Genitourinary
Steroid use
eGFR <45 mL/min/1.73m^2
Platelet count <100 x 10^3/μl
BUN >30 mg/dL
RDW >14.5%
Serum potassium <4.0 mmol/L
Hemoglobin <11.5 g/dL

BUN=blood urea nitrogen; CI=confidence interval; CVC=central venous catheter; eGFR=estimated glomerular filtration rate; GCS=Glasgow coma scale; OR=odds ratio; RDW=red cell distribution width

[a]Chiang HY, Chen TC, Lin CC, et al. Trend and Predictors of Short-Term Mortality of Adult Bacteremia at Emergency Departments: A 14-Year Cohort Study of 14,625 Patients. *Open Forum Infect Dis*. 2021; 8(11):ofab485.

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