

Staphylococcus Aureus Bacteremia Due to Central Venous Catheter Infection: A Clinical Comparison of Infections Caused by Methicillin-Resistant and Methicillin-Susceptible Strains

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Abstract

Background: Staphylococcus aureus (*S.aureus*) bacteremia has a mortality rate ranging from 20-40%. Central venous catheter (CVC) infection is the leading cause of *S.aureus* bacteremia. We investigated the differences in background characteristics, complications, and prognosis between patients with methicillin resistant *S.aureus* (MRSA) and methicillin sensitive *S.aureus* (MSSA) bacteremia due to CVC infection.

Methods: We retrospectively investigated patients who had positive peripheral blood cultures versus positive semi-quantitative cultures for MRSA or MSSA from the CVC tip. We compared the clinical background characteristics, complications, and 60-day mortality rates between both groups. We analyzed our data using Mann-Whitney U test, chi-square test, and Fisher's exact test.

Results: This study had 17 (47%) and 19 (53%) MRSA and MSSA bacteremia patients, respectively. The median ages for MRSA and MSSA patients were 72 ± 27 and 55 ± 33 years, respectively ($P < 0.01$). Comparison between baseline disease occurrence (MRSA vs. MSSA) was 10(59%) patients vs. 3(16%) patients ($P = 0.01$), while complications included septic shock were 8(48%) vs. 3(16%) ($P = 0.07$), respectively. The duration of catheter placement, time lag from onset of fever to CVC removal, and time lag from onset of fever to starting antimicrobial therapy were similar in both groups. Sixty-day mortality rates were 35%(6/17) vs. 5.3%(1/19), ($P = 0.04$), in MRSA vs. MSSA groups, respectively.

Conclusions: MRSA carriers and older patients were at a higher risk of MRSA CVC infection compared to MSSA bacteremia patients. MRSA bacteremia patients showed relatively higher rate of septic shock, and had significantly higher 60-day mortality rate despite appropriate antimicrobial therapy.

Background

Approximately 20–50% of *S.aureus* isolated in Japanese medical facilities is MRSA; one of the major resistant bacteria [1]. The risk factors for *S.aureus* bacteremia include central venous catheter (CVC), solid tumor, chronic kidney disease, history of hospitalization, and prolonged antimicrobial use.

CVC infection caused by *S.aureus* is a major cause of *S.aureus* bacteremia and is an important healthcare associated infection [2,3]. Generally, the mortality rate of *S.aureus* bacteremia is 20–40%, and there are many studies that report MRSA bacteremia showing higher mortality rate than MSSA bacteremia. There are few studies, however, that investigated the differences and prognosis comparing MRSA bacteremia patients with MSSA bacteremia patients, secondary to CVC infection. The purpose of this study was to investigate the differences of clinical backgrounds, complications and prognosis, comparing MRSA bacteremia patients with MSSA bacteremia patients, secondary to CVC infection at St. Luke's International Hospital.

Methods

We retrospectively investigated all patients who positive for MRSA or MSSA from peripheral blood cultures and positive from semiquantitative cultures from CVC tip taken on the same day or on a close day (within 3 days from the day of positive blood cultures) between August 2004 to March 2016 at St Luke's International Hospital. This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (Number: 16-J011). Due to retrospective nature of the study, informed consent was waived by the Institutional

Review Board of St. Luke's International Hospital. We included patients aged over 15 years, with sufficient medical records, and diagnosed with primary CVC infection. A positive semiquantitative culture was defined as 15 colonies or more found. We excluded patients with secondary *S.aureus* bacteremia and end stage malignancy.

We retrospectively reviewed patient medical records. The primary outcome was death from infection within 60 days of CVC removal. In this study, we investigated the following clinical factors, comparing them between MRSA and MSSA bacteremia patients: baseline characteristics, age (patients ≥ 65 years were defined as elderly), sex, MRSA carrier, baseline diseases, ICU admission during hospitalization, surgery, total parenteral nutrition (TPN), steroid use, chemotherapy, immunosuppressant use, and complications such as endophthalmitis, infective endocarditis, deep abscess, septic shock, antimicrobial treatment, duration of CVC replacement, time lag from the day of symptom onset of the infection (fever in most cases) to the day of CVC removal, and time lag from symptom onset to the day of starting effective antimicrobial therapy (Cloxacillin or Cefazolin for MSSA, and Vancomycin(VCM) or Daptomycin for MRSA). We also investigated mortality rates within 60 days from the day of removal of the infected CVC and compared them between MRSA and MSSA bacteremia patients.

The statistical method was divided into MRSA patients group and MSSA patients group. In the univariate analysis, Mann-Whitney test was used for continuous variables, and χ^2 test and Fisher's exact test were used for categorical variables. The primary outcome was death within 60 days of CVC removal, and multivariate analysis was performed on MRSA, age, and sex.

As a sub-analysis, we investigated the minimum inhibitory concentration (MIC; $\mu\text{g/ml}$) of VCM in each MRSA strain isolated from MRSA bacteremia patients who received VCM. We compared the VCM MIC values of MRSA between patients who died and those who survived from MRSA bacteremia, secondary to CVC infection. We also investigated the relationship between VCM MIC values and prognosis of MRSA bacteremia, secondary to CVC infection.

Results

Forty-nine patients with *S.aureus* bacteremia were observed between August 2004 to March 2016. We excluded 4 patients with other primary sites infections and 9 patients with end-stage malignancy. Total 36 patients with *S.aureus* bacteremia due to CVC infection were identified and met the final inclusion criteria for analysis. Out of these 17 (47%) were MRSA bacteremia patients and 19 (53%) were MSSA bacteremia patients (Fig. 1).

Table 1 showed the baseline characteristics of patients with *S.aureus* (MSSA, MRSA) central venous catheter infection.

Table 1
Baseline characteristics of the patients with *S.aureus* CVC infection(N = 36), univariate analysis of MSSA bactremia patients(N = 19) versus MRSA bacteremia patients(N = 17)

	S.aureus (N = 36)	MSSA (N = 19)	MRSA (N = 17)	P-value
Age: median(IQR) years	64(± 19)	55(± 33)	72(± 27)	0.01
Age(> 65), n(%)	16(44)	6(32%)	10(59%)	0.10
Male, n(%)	16(44)	10(53)	6(35)	0.30
MRSA carrier, n(%)	13(36)	3(15.8)	10(58.8)	0.01
Diabetes mellitus, n(%)	8(22)	5(26)	3(18)	0.70
Malignancy, n(%)	7(19)	5(26)	2(12)	0.41
Hematological malignancy, n(%)	6(16.7)	2(11)	4(24)	0.39
Post-transplant, n(%)	2(5.6)	0(0)	2(12)	0.22
Renal disease, n(%)	11(31)	7(37)	4(24)	0.48
Liver disorder, n(%)	2(5.6)	1(5.3)	1(5.9)	1.0
Cerebrovascular disease(%)	8(22)	5(26)	3(18)	0.70
ICU stay, n(%)	12(33)	6(32)	6(36)	1.0
Post-surgery, n(%)	8(22)	4(22)	4(24)	1.0
Total parenteral nutrition, n(%)	17(47)	7(37)	10(60)	0.32
Steroid user, n(%)	12(33)	4(22)	8(48)	0.16
Chemotherapy, n(%)	4(11)	3(16)	1(5.9)	0.61
Immunosuppressant, n(%)	4(11)	1(5.3)	3(18)	0.33

The median age of all the patients was 64 years (interquartile range: IQR: 45–83 years), Median age of MRSA patients was 72 ± 27 years and median age of MSSA patients was 55 ± 33 years (P < 0.01). The median age was significantly higher in MRSA bacteremia patients than in MSSA bacteremia patients, and elderly patients might have a higher risk of MRSA bacteremia secondary to CVC infection compared with patients of younger age.

Thirty-five % of the MRSA bacteremia patients were male and 53 % of the MSSA bacteremia patients were male, (P = 0.30).

The results of baseline diseases of the two groups of patients were as follows: MRSA carrier: 10 MRSA patients (59%) vs 3 MSSA patients (16%) (P = 0.01), diabetes mellitus: 3 (18%) MRSA patients vs 5 MSSA patients (26%) (P = 0.70), malignancy: 2 MRSA patients (12%) vs 5 MSSA patients(26%)(P = 0.41), renal diseases: 4 MRSA patients (24%) vs 7 MSSA patients(37%)(P = 0.48), steroid use: 8 MRSA patients (48%) vs 4 MSSA patients (22%)(P = 0.16), and TPN: 10 MRSA patients (60%) vs 7 MSSA patients (37%),(P = 0.32).

There was not a significant difference in baseline diseases between the MRSA bacteremia patients and MSSA bacteremia patients.

Complications found in the two group of patients were as follows(Table 2): Septic shock: 8 MRSA patients (48%) vs 3 MSSA patients (16%), (P = 0.07),and infective endocarditis: 0 MRSA patients (0%) vs 2 MSSA patients (11%), (P = 0.49), MRSA patients showed relatively higher rate of complication of septic shock compared with MSSA patients.

Table 3 shows the management of CVC infection in MSSA and MRSA groups. The duration of catheter placement in the two groups were as follows: MRSA patients: 13.5 ± 8 days vs MSSA patients: 9.5 ± 20 days,(P = 0.58). The time lag from onset of fever to CVC removal in the two groups were as follows: MRSA patients: less than 1.0 day vs MSSA patients 1.0 day,(P = 0.71). Time lag from onset of fever to start effective antimicrobial therapy of the two group of the patients was as follows:(All the MRSA patients were treated with VCM.) MRSA patients less than 1 day vs MSSA patients less than 1 day,(P = 0.7),

There was no difference between the MRSA patients and MSSA patients in duration of catheter placement, time lag from onset of fever to CVC removal and time lag from onset of fever to start effective antimicrobial therapy between MRSA patients and MSSA patients.

Eight patients (19%:8/36) died due to CVC-associated *S.aureus* bacteremia (MRSA or MSSA) within 60 days from the day of CVC removal. Out of these 6 patients (35%:6/17) died due to MRSA bacteremia, and 1 (5.3%:1/19) died due to MSSA bacteremia). The 60-day mortality rate was significantly higher in MRSA patients compared with MSSA patients (35% vs 5.3%, P = 0.04).

Table 2
Univariate analysis of complications and prognosis of the MSSA bacteremia patients versus the MRSA bacteremia patients.

	S.aureus (N = 36)	MSSA (N = 19)	MRSA (N = 17)	P-value
Endophthalmitis, n(%)	3(8.3)	1(5.3)	2(12)	0.59
Infective Endocarditis, n(%)	2(5.6)	2(11)	0(0)	0.49
Deep abscess, n(%)	2(5.6)	0(0)	2(12)	0.22
Septic shock, n(%)	11(31)	3(16)	8(48)	0.07
60-day mortality rate, n(%)	7(19)	1(5.3)	6(35)	0.04

Table 3
Univariate analysis of treatment of the MSSA bacteremia patients vs MRSA bacteremia patients

	S.aureus (N = 36)	MSSA (N = 19)	MRSA (N = 17)	P-value
Duration of CVC placement, median(IQR)	9.5(20)	9.5(20)	13.5(8)	0.58
Time lag from onset to CVC removal, median(IQR)	1.0(3)	1.0(3)	0.0(7)	0.71
Time lag from onset to start effective antibiotics, median(IQR)	0.0(2)	0.0(2)	0.0(3)	0.07

Table 4
Multivariate analysis of risk factors of 60-day mortality rate from CVC removal with adjustments for MRSA, aged over 65 and male.
OR: Odds Ratio

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
MRSA	9.8(1.0–93)	0.05	8.2(0.81-83)	0.08
Age(> 65)	1.9(0.36-10)	0.46	1.4(0.2–10)	0.71
Male	0.4(0.07–2.6)	0.36	0.5(0.06–3.8)	0.49

Table 4 shows the results of multivariate analysis of risk factors of 60-day mortality rate from CVC removal with adjustments for MRSA, males aged over 65 years. There was no statistically significant difference between the two groups, but in the 60-day mortality of MRSA bacteremia patients compared with MSSA bacteremia patients, the adjusted odds ratio (OR) was 8.2 (95% CI 0.81-83; p = 0.08), which was lower than crude OR [9.8, (95%CI 1.0–93; p = 0.05)].

As a sub-analysis, we investigated the VCM minimum inhibitory concentration (MIC:µg/ml) value of the MRSA strains isolated from 7 MRSA bacteremia patients who died within 60 days after CVC removal, and MRSA strains isolated from the 10 MRSA bacteremia patients who survived, and compared the two groups (Table 5). We also investigated the relationship between VCM MIC value of MRSA isolated from the patients and 60-day survival rate of MRSA bacteremia patients.

Table 5
VCM MIC value (µg/ml) of MRSA isolated from 17 MRSA bacteremia patients comparing between the 7 patients who died and the 10 patients who survived and the 60-day survival rate after CVC removal.

VCM MIC(µg/ml)	Patients who died (n = 7)	Patients who survived (n = 10)	Total (n = 17) (% of total MRSA)	60-day survival rate(%)
2.0	3	1	4(23%)	25%
1.0	1	1	2(12%)	50%
less than 1.0	3	8	11(65%)	73%

In the MRSA group (n = 17), all the 17 patients were treated with VCM from the beginning. VCM MIC results for MRSA isolated from all 17 patients were as follows: MIC < 1.0 µg/ml:4 patients (65%:11/17), MIC = 1.0 µg/ml:2 patients

(12%:2/17), MIC = 2.0 µg/ml: 4 patients (23%:4/17). The results of VCM MIC of MRSA isolated from the patients who died were as follows: MIC 2.0 µg/ml:3 patients (43%:3/7), MIC 1.0 µg/ml:1 patient (14%:1/7), MIC < 1.0 µg/ml:3 patients (43%:3/7). The results of VCM MIC of MRSA isolated from the patients who survived were as follows: MIC 2.0 µg/ml:1 patient (10%:1/10), MIC 1.0 µg/ml:1 patient (10%:1/10), MIC < 1.0 µg/ml:8 patients (80%:8/10).

73 % of the patients (8/11) who had MRSA bacteremia with VCM susceptible strain (MIC < 1.0 µg/ml) survived, and 27% of the patients died. Fifty percent survival was observed in patients (1/2) who had MRSA bacteremia with moderate susceptibility to VCM (MIC = 1.0 µg/ml). On the other hand, 25% survival was observed in patients (3/4) who had MRSA bacteremia with reduced VCM susceptibility (MIC = 2.0 µg/ml).

These results suggested that prognosis of patients with MRSA bacteremia due to CVC infection might be related to VCM MIC value. This result was, however, not statistically significant because of small number of patients.

Discussion

The results of this study showed high susceptibility of MRSA patients with MRSA CVC infection were significantly older than the patients with MSSA CVC infection, and MRSA CVC infection was observed at significantly higher rate in MRSA carrier patients compared with non-MRSA carrier patients.

There was not a significant difference in baseline diseases between the MRSA bacteremia patients and MSSA bacteremia patients.

In both MRSA bacteremia patients and MSSA bacteremia patients, infected CV catheters were removed early and effective antimicrobial agents was started early without significant differences in the two group.

The patients with MRSA bacteremia showed significantly higher 60-day mortality rate (35%) than patients with MSSA bacteremia (5.3%), (P = 0.04).

Additionally, worse prognosis was found in MRSA bacteremia patients infected with a strain less susceptible to VCM (MIC 2.0 µg/ml, which is the upper limit of VCM susceptibility), who were treatment with VCM (mortality rate 75%:3/4), compared with patients who had MRSA bacteremia caused by VCM susceptible strain (MIC < 1.0 µg/mL) (mortality rate 27%:3/11) [5–9]. This result, however, is not statistically significant due to the small sample size. More studies with larger sample size are required.

Further study will be needed to investigate whether the patients with MRSA bacteremia due to CVC infection caused by MRSA with VCM reduced susceptibility strain (MIC = 2.0 µg/ml) would have worse prognosis compared with the patients who had MRSA bacteremia with VCM susceptible strain (MIC < 1.0 µg/ml) under VCM therapy.

According to the Infectious Diseases Society of America (IDSA) guidelines [4], Daptomycin 6 mg/kg/day or VCM is recommended as the first line therapy for uncomplicated MRSA bacteremia without infective endocarditis.

However, it has been reported that VCM is less effective than β -lactam antibiotics (Cefazolin, Cloxacillin, etc.) for treating MSSA bacteremia, and its bactericidal activity might be weaker than that of β -lactam antibiotics [10].

In future, we should investigate whether prognosis could be improved by using Daptomycin, which could have stronger antibacterial activity, especially against MRSA infection with the reduced VCM susceptibility strain. We also need to investigate how much dosage of Daptomycin would be appropriate to treat CVC MRSA bacteremia.

In the multivariate analysis, the MRSA group showed no statistically significant difference in the 60-day mortality rate, but the adjusted OR was lower than the crude OR. In this study, the number of samples was small, but it was suggested that there might be other risk factors for death within 60-day mortality other than MRSA. A previous study on *S.aureus* infections showed that severities, such as septic shock, might be important risk factors [3], which should be discussed for future studies.

This study had imitations. First, the method of extracting CVC infection patients from our database. We extracted data according to the CVC infection as defined by the Catheter-Related Bloodstream Infections (CRBSI) guidelines from IDSA [11] or the Central Line Associated Bloodstream Infection (CLABSI) from the Centers for Disease Control and Prevention (CDC) [12]. However, at St. Luke's International Hospital, the definition of CVC infection became available among clinicians after 2014, when Differential Time to Positivity (DTP) and quantitative culture were used. In this study, the definition of CVC infection was that central catheter such as CVC, CV port and PICC was placed in the central vein and that *S.aureus* was detected with simultaneously blood culture and catheter tip using semiquantitative culture.

In addition, this was a single-center retrospective study and thus, there might be selection bias. Moreover, few CVC infections samples were available thus, the variables of multivariate analysis were limited. In future, prospective observational research at multiple facilities using CRBSI and CLABSI should be conducted.

Conclusion

MRSA bacteremia patients with secondary CVC infection might have a high 60-day mortality rate compared to MSSA bacteremia patients under antimicrobial therapy with VCM. Measures to prevent CVC infection due to MRSA and early and a more effective antimicrobial therapy would be future challenges.

Abbreviations

CVC: central venous catheter

MRSA: methicillin sensitive *S.aureus*

MSSA: methicillin sensitive *S.aureus*

VCM: Vancomycin

MIC: minimum inhibitory concentration

IQR: Interquartile range

IDSA: Infectious Diseases Society of America

CRBSI: Catheter-Related Bloodstream Infections

CLABSI: Central Line Associated Bloodstream Infection

CDC: Centers for Disease Control and Prevention

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (Number: 16-J011). Due to retrospective nature of the study, informed consent was waived by the Institutional Review Board of St. Luke's International Hospital. We will comply with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects, and give consideration to the protection of human rights. Since this research is an observational study using existing samples and information, there will be no direct intervention on the subject individuals, and the human rights of the individuals will be protected.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The manuscript was seen and approved by all the authors and is not under consideration elsewhere. All the authors contributed to the work in this report. KI collected clinical data and wrote the initial draft of the manuscript. EH and KF supervised and edited the manuscript. The author(s) read and approved the final manuscript.

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Figures

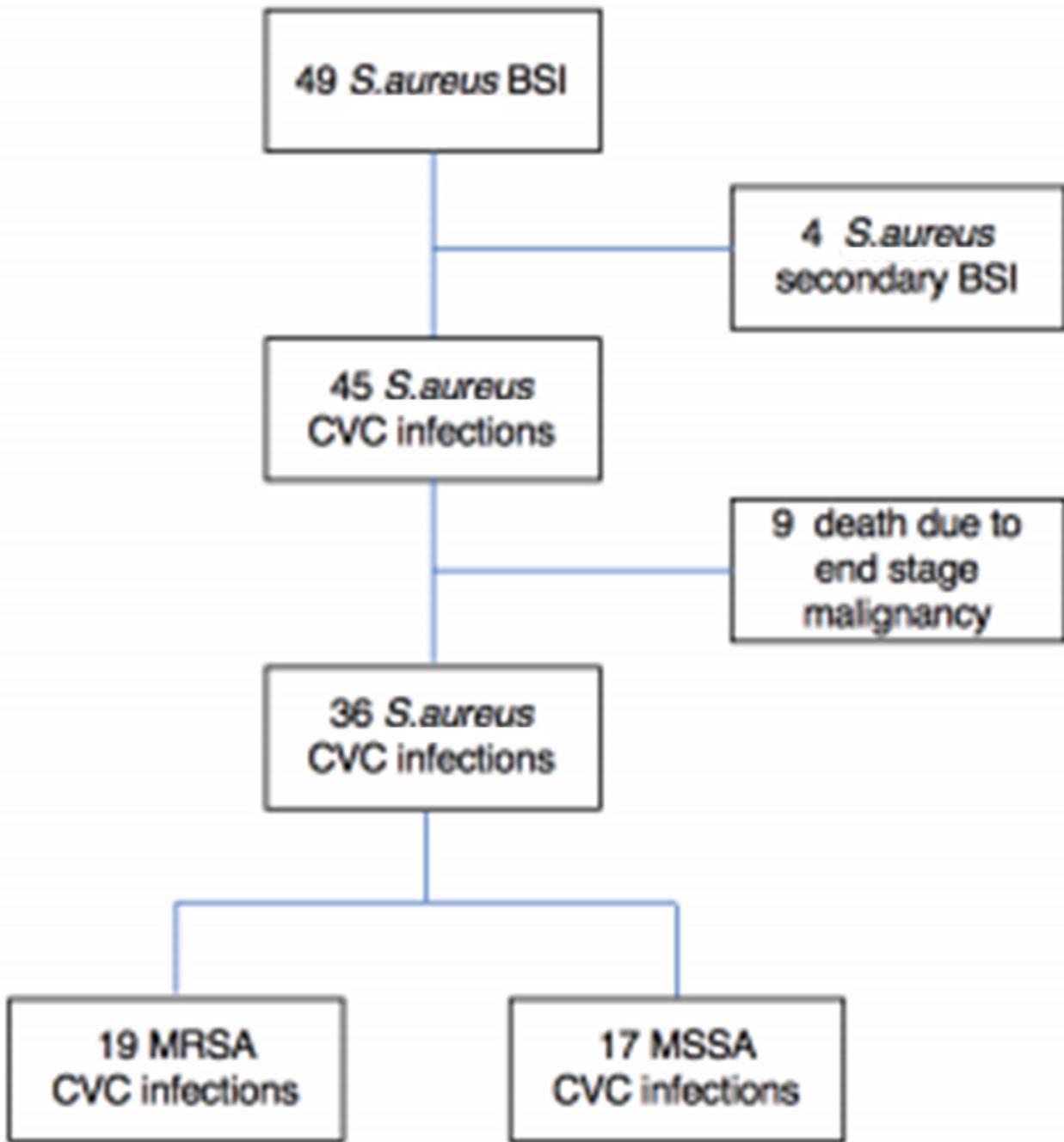


Figure 1

Process for identification of the patients with *S.aureus* bacteremia due to central venous catheter infection at St. Luke's International Hospital from Aug 2004 to Mar 2016.