

Distribution characteristics of *Staphylococcus* spp. in different phases of periprosthetic joint infection: A review (Review)

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Abstract. Periprosthetic joint infection (PJI) is a devastating condition and *Staphylococcus* spp. are the predominant pathogens responsible, particularly coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*. The aim of the present systematic review was to evaluate the distribution characteristics of specific *Staphylococcus* spp. in different PJI phases, reveal the effect of pathogens' feature on their distribution and suggest recommendations for antibiotic treatment of Staphylococcal PJI. The present systematic review was performed using PubMed and EMBASE databases with the aim to identify existing literature that presented the spectrum of *Staphylococcus* spp. that occur in PJI. Once inclusion and exclusion criteria were applied, 20 cohort studies involving 3,344 cases in 3,199 patients were included. The predominant pathogen involved in PJI was indicated to be CoNS (31.2%), followed by *S. aureus* (28.8%). This trend was more apparent in hip replacement procedures. In addition, almost equal proportions of CoNS and *S. aureus* (28.6 and 30.0%, respectively) were indicated in the delayed phase. CoNS (36.6%) were the predominant identified organism in the early phase, whereas *S. aureus* (38.3%) occurred primarily in the late phase. In PJI caused by *S. aureus*, the number of cases of methicillin-sensitive *Staphylococcus aureus* (MSSA) was ~2.5-fold greater than that of methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA occurred predominantly in the early phase, whereas MSSA was largely observed in the delayed and late phases. With regards to antibiotic treatment, the feature of various pathogens and the phases of PJI were the primary considerations. The present review provides useful information for clinical practice and scientific research of PJI.

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1. Introduction

Various studies have indicated that the incidence of periprosthetic joint infection (PJI), following total joint arthroplasty (TJA), ranged between 0.5 and 2% for primary knee arthroplasty and 0.2 to 1.3% for primary hip replacement (1-5); however, when considering revision surgery, the infection risks were elevated markedly (4,6). For the past few decades, various effective strategies, such as the use of laminar airflow, body exhaust suits, prophylactic antibiotics (intravenous antibiotics and antibiotic-loaded cement) and minimizing operating room traffic, have all contributed to reducing infection rates in general (4,6-10). Despite this, the total number of infections following TJA have been significantly increasing over the past few years (1,3,11) as a result of the continuously increasing arthroplasties required among the elderly (10,12,13). Once established, PJI is a disastrous condition for patients and is a serious economic burden to the healthcare system (1,3,4,6,7,10,14-16).

As previously reported, *Staphylococcus* spp. are the predominant causative organisms associated with PJI, particularly coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, which comprise 50-80% of all isolates (12,16-25). However, the variant species of *Staphylococcus* differ from one another in virulence, antibiotic resistance and biofilm formation ability, thus have individual distribution characteristics in different phases of PJI. On the basis of the PJI classification system proposed by Zimmerli *et al* (26), the early phase PJI, presenting within 3 months, are typically caused by virulent bacteria such as *S. aureus* and gram-negative bacilli, whereas delayed PJI, presenting between 3 and 24 months, are commonly caused by less virulent pathogens such as CoNS and *Propionibacterium acnes* (26).

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As a critical pathogen of CoNS, the incidence of methicillin-resistant *Staphylococcus epidermidis* (MRSE) (2,9,23,27-29) has increased significantly in PJI over the past two decades (27,29-33), which may be associated with the use of prophylactic antibiotics (32). However, whether MRSE is able to cause the distribution changes in the phases of PJI has not been studied until now. Similarly, *S. aureus* may be classified into two categories: Methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). Due to differences in antibiotic resistance, discrepancies appear in the occurrence, treatment and prognosis of MSSA and MRSA (19,34-36). However, few studies have reported the discrepancy of the incidence between MSSA and MRSA in PJI (15,34,35). In the present review, literature concerning PJI in recent decades was reviewed to interpret the distribution characteristics of *Staphylococcus* spp. in different PJI phases and investigate the influence of pathogens' virulence and antibiotic resistance on distribution changes. Furthermore, the present review suggests recommendations for antibiotic treatment, dependent on the feature of various pathogens and the phases of PJI.

2. Materials and methods

Search methods. The present systematic review of published studies was performed without language limitation using the most common databases, PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) and EMBASE (<https://www.embase.com/#search>). The key words used were: 'Staphylococcus', 'infection', 'revision', 'knee arthroplasty/replacement', 'hip arthroplasty/replacement', 'joint arthroplasty/replacement', 'arthroplasty, replacement, knee/hip' and 'arthroplasty, replacement'. Studies published prior to June 30, 2015 were searched.

Inclusion and exclusion criteria. Inclusion criteria were: Patients undergoing a PJI or deep infection following knee or hip arthroplasty; and microbiology of the infected arthroplasty that involved staphylococcal species. Exclusion criteria were: Animal or *in vitro* experiments and the surgical sites of PJI or deep infection did not include the knee or hip; the spectrum of staphylococci was not reported; and data extraction from the studies was difficult.

Data collection, extraction, management and analysis. The titles and abstracts of all studies were screened carefully and the potentially eligible studies were elected by one author. Subsequently, two reviewers critically analyzed the full texts of the selected studies. Every contradiction was resolved by group discussion directed by one author.

In the present review, the classification system for PJI proposed by Zimmerli *et al* (26) was used. According to this classification system, PJI should be classified into three phases: early, presenting within 3 months; delayed, between 3 and 24 months; and late, over 24 months (1,2,11,13,25,26,31,37). Relevant data of included studies were extracted independently by two investigators and verified by another. The extracted data included: Authors, year of publication, study design, study period, number of cases and patients, mean age, gender, surgery site, phase of PJI and spectrum of causative microorganisms.

All data were collected in specifically designed Microsoft Office Excel spreadsheets. According to the same inclusion criteria proposed by Zimmerli *et al* (26), data was pooled from various included studies in order to compensate for the deficiency of the single study.

In order to observe the distribution characteristics of *Staphylococcus* spp. in the knee and hip, stratification analysis was performed according to the surgery site type (hip or knee). Subsequently, when the distribution characteristics of bacteria in different infection phases were analyzed, the previous inclusion criteria were modified by adding the following criteria: i) PJI was classified according to Zimmerli *et al* (26) or could be converted to the criteria; and ii) having corresponding pathogens in three different phases of PJI. Consequently, eligible documents were selected among the included studies. Analogously, when the percentages of MSSA and MRSA were compared, studies were chosen based on the availability of the classification information of *S. aureus*.

Statistical methods. SAS software (Release 8.02 TS Level 02M0; SAS Institute, Inc., Cary, NC, USA) was used to perform statistical analysis. The frequencies and percentages of the pathogens were calculated and analyzed in the included studies and merged data. The Pearson χ^2 test was used to assess the distribution of microbiological findings. $P < 0.05$ was considered to represent significant differences.

3. Results

Description of the selected studies. Due to duplications between PubMed and EMBASE, 447 articles were excluded among 1,025 eligible studies identified in the initial literature retrieval. Subsequently, 520 were refused by screening the titles and abstracts. The remaining 58 studies, including an additional 19 studies added from a reference review, were in entirety read and 56 articles were eliminated for not meeting the inclusion criteria. Subsequently, the remaining 20 articles were included in the present systematic review after one unsuitable research article was rejected as the necessary data extraction was difficult. According to the new inclusion criteria, four studies were selected and used to observe the distribution characteristics of *Staphylococcus* spp. in different PJI phases. A total of 10 studies were used to analyze the categorization features of *S. aureus* in PJI. A flow chart of the selection process is shown in Fig. 1.

General characteristics of included studies. The 20 included studies involved 3,344 cases in 3,199 patients following joint arthroplasty, including 1,630 knee, 1,700 hip and 14 others, such as ankle, shoulder and elbow cases. All of these identified studies were retrospective/prospective cohort studies in this search. The sample size of the included studies varied from 15 to 785 cases between the years of 1974 to 2013. The general characteristics and patient demographics of the included studies are displayed in Table I.

Among the 20 studies, six studies (1,8,33,38-40) reported knee cases, five (9,32,41-43) reported hip cases and nine (2,6,12,13,19,20,27,28,44) reported knee and hip cases. Of the nine studies, four articles (6,12,28,44) were divided into two categories of knee and hip cases on the basis of the type

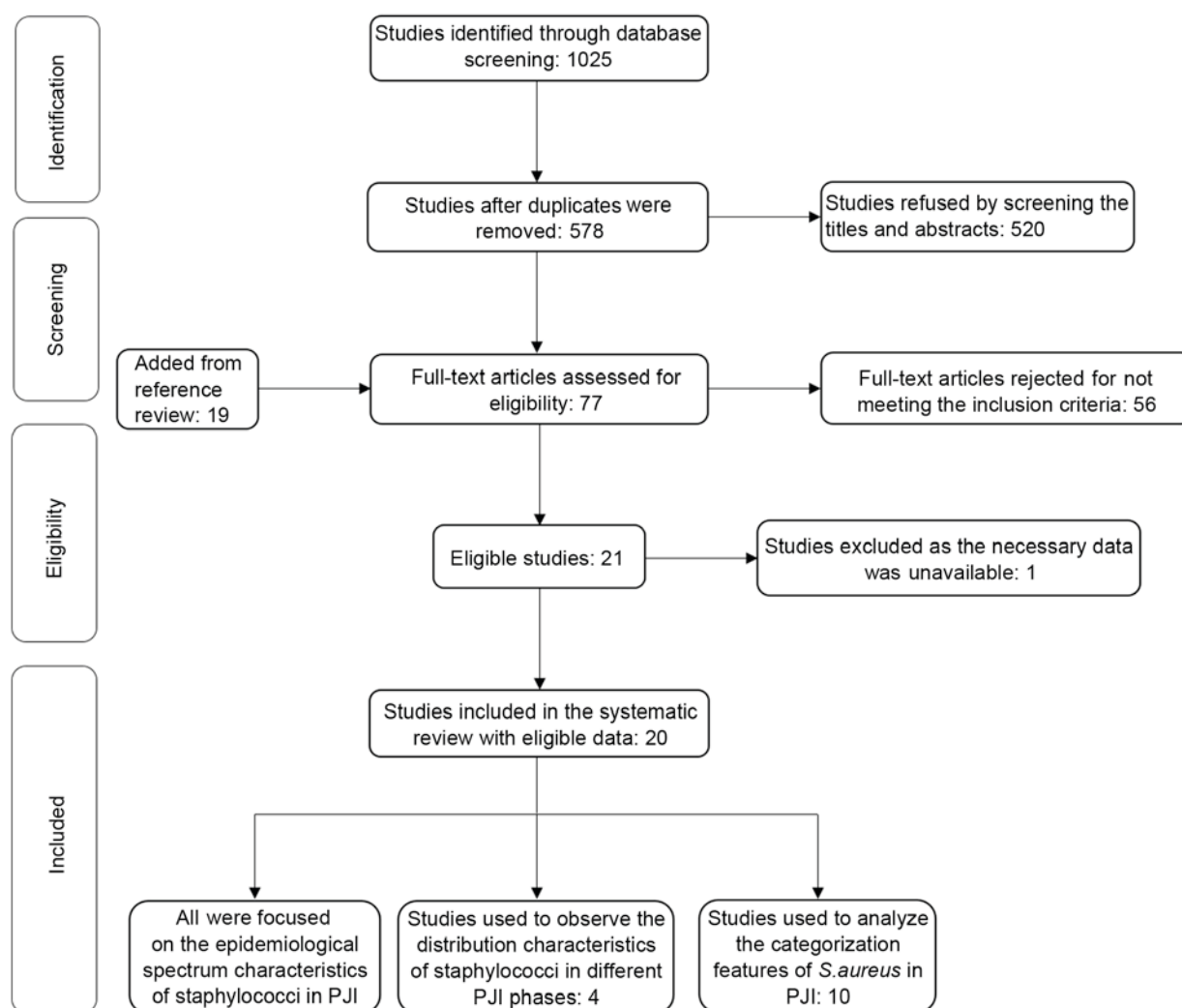


Figure 1. Flow chart of selection process in the systematic review. PJI, periprosthetic joint infection.

of staphylococci, whereas the other five studies (2,13,19,20,27) were not. Furthermore, a small fraction of polymicrobial infection that occurred in a number of studies (1,2,9,12,13,20,27,38,39,41) was converted to the monomicrobial infection for calculating the percentage of sole pathogens in the present review.

Incidences of *Staphylococcus* in 20 included studies. In the 20 included studies, CoNS (11.1-67.1%) and *S. aureus* (0.0-54.9%) were the predominant organisms in PJI following joint arthroplasty, as presented in Table II. The pooled rates of CoNS and *S. aureus* were 31.2 and 28.8%, respectively, which together accounted for 60.0% of the total isolated organisms. Furthermore, the rates of CoNS isolated from knee cases ranged from 7.1 to 66.7% in 10 studies, with a pooled rate of 28.1%. However, the incidences of *S. aureus* varied from 0.0 to 50.0%. The merged rate was 27.5%. Likewise, CoNS were cultured from hip cases in nine studies, with rates ranging from 13.6 to 67.1%. The pooled rate was 34.7%. *S. aureus* incidence in PJI ranged from 12.9 to 51.7%, with a merged rate of 25.4% in the hip. It was apparent that the most frequently encountered microorganism was CoNS, followed by *S. aureus* in total knee arthroplasty (TKA) or total hip arthroplasty (THA). Overall,

the distributions of CoNS and *S. aureus* were similar (31.2 and 28.8%, respectively) in PJI. However, CoNS was indicated to be more common in the hip (34.7%) than in the knee (28.1%; $P=0.004$).

Incidences of *Staphylococcus* in different phases of PJI. As classified by the occurring time of PJI in Table III, 524 infected cases in four studies (1,2,28,39) were identified and met the new inclusion criteria. The occurrence rates of infections were indicated to be 29.2% in the early phase, 41.4% in the delayed phase, and 29.4% in the late phase. Of the three phases, CoNS and *S. aureus* (41.6 and 41.7%, respectively) were distributed predominantly in the delayed phase. In terms of the sole microorganism detected within each respective phase there was a similar proportion of CoNS and *S. aureus* (28.6 and 30.0%, respectively) in the delayed phase. When comparing CoNS and *S. aureus*, CoNS (36.6%) was determined as the predominant organism in the early phase, whereas *S. aureus* (38.3%) was detected primarily in the late phase ($P<0.001$).

Comparison of MSSA and MRSA in 10 included studies. Among the included studies, 10 studies (2,13,19,27,28,33,40,41,43,44), involving 510 cases in 1,587 patients infected with

Table I. General characteristics and patient demographics in 20 included studies.

Author, year	Study period	Study design	Cases (N)	Patients (N)	Gender (F/M)	Mean age (years)	Surgery site (N)	(Refs.)
							Knee/Hip/ Others	
Wilde <i>et al.</i> , 1988	1980-1987	PCS	15	15	7/8	68.0	15/0/0	(39)
Burger <i>et al.</i> , 1991	1976-1988	RCS	39	39	ND	ND	39/0/0	(38)
Giulieri <i>et al.</i> , 2004	1985-2001	PCS	63	60	20/40	72.0	0/63/0	(42)
Ip <i>et al.</i> , 2005	1995-2003	RCS	36	36	12/24	70.0	14/22/0	(28)
Fulkerson <i>et al.</i> , 2006	1991-2003	RCS	194 ^a	146	82/64	66.0	84/110/0	(12)
Phillips <i>et al.</i> , 2006	1987-2001	PCS	75	75	38/37	67.6	41/34/0	(2)
Rafiq <i>et al.</i> , 2006	1974-2005	RCS	255	255	ND	ND	0/255/0	(9)
Moran <i>et al.</i> , 2007	1998-2003	RCS	112	112	50/62	68.8	51/52/9	(27)
Sharma <i>et al.</i> , 2008	1999-2006	RCS	248 ^a	147	ND	ND	108/140/0	(6)
Stefansdottir <i>et al.</i> , 2009	1986-2000	RCS	426	426	244/182	Primary 68.1 revision 70.9	426/0/0	(1)
Teterycz <i>et al.</i> , 2010	1996-2008	RCS	82	82	39/43	69.0	29/52/1	(19)
Nickinson <i>et al.</i> , 2010	1994-2008	RCS	121	121	60/61	71.0	121/0/0	(8)
Tsai <i>et al.</i> , 2015	2006-2011	RCS	144	144	81/63	68.9	88/52/4	(13)
Kuiper <i>et al.</i> , 2013	2004-2009	RCS	91	91	54/37	70.0	29/62/0	(20)
Lutro <i>et al.</i> , 2014	1993-2007	PCS	278	278	188/90	67.6	0/278/0	(32)
Ibrahim <i>et al.</i> , 2014	2000-2008	PCS	125	125	74/51	68.0	0/125/0	(41)
Bjerke-Kroll <i>et al.</i> , 2014	1998-2011	RCS	785	793	355/438	TKA 65.6 THA 65.3	390/395/0	(44)
Holmberg <i>et al.</i> , 2015	2000-2008	PCS	145	144	62/82	70.0	145/0/0	(40)
Matsumoto <i>et al.</i> , 2015	2000-2010	RCS	50	50	12/38	71.1	50/0/0	(33)
Triantafyllopoulos <i>et al.</i> , 2015	2001-2013	RCS	60	60	31/29	64.9	0/60/0	(43)
Total			3,344	3,199			1,630/1,700/14	

^aCases were positive specimens isolated from knee or hip. F, female; M, male; PCS, prospective cohort study; RCS, retrospective cohort study; ND, no data; primary, primary arthroplasty; revision, revision arthroplasty; TKA, total knee arthroplasty; THA, total hip arthroplasty.

S. aureus, were selected to provide the classification information of *S. aureus*. The ratios of MSSA and MRSA varied from 9 to 633%. The merged ratio was 262%. A clear trend was observed where the number of MSSA was ~2.5-fold greater than that of MRSA in PJI caused by *S. aureus*. Fig. 2 summarizes the detailed information.

4. Summary and interpretation of main results

CoNS may be more common than S. aureus, particularly in hip PJI. As a principal part of the skin and mucous membrane microflora (8,45,46), constituting 65-90% of all staphylococci, CoNS are commonly encountered in clinical settings, particularly during orthopedic surgery. In an article researching intraoperative bacterial contamination during joint replacement, Davis *et al.* (45) discovered CoNS were involved in 76% of 776 gathered samples. Equally, CoNS were identified in 77% of contaminated femoral heads, which were donated during primary hip arthroplasty (47).

Arciola *et al.* (21) and Montanaro *et al.* (22) conducted two large studies concerning orthopaedic infections. In infections associated with medical devices, the prevalence of

Staphylococcus epidermidis was observed to have increased from 31.5% in the previous collection (between 2000 and 2003) to 39.0% in the new collection (between 2007 and 2011), and the incidence of *S. epidermidis* was greater than *S. aureus* (39.0 and 31.7%, respectively) (16,22). These studies revealed that CoNS were progressively prevailing when compared with *S. aureus* (22). Moreover, *S. epidermidis* was the dominating bacteria identified in infections associated with knee and hip arthroplasties, whereas *S. aureus* was predominantly exhibited in infections associated with no medical devices and fracture fixation devices (22). These evidences suggest that CoNS were more common than *S. aureus* in PJI.

Compared with primary or revision TKA, patients undergoing primary or revision THA tended to be older, sicker and required a longer length of stay in hospital (36,48), indicating that patients who underwent TKA generally had a stronger ability to resist CoNS, a less virulent pathogen, when compared with patients who underwent THA. Moreover, in THA infection, Lutro *et al.* (32) demonstrated that CoNS (41%) were more frequent than *S. aureus* (19%) and exhibited a significant increase in resistance to nearly all antibiotics (except for linezolid and vancomycin), whereas *S. aureus* and other bacteria exhibited

Table II. Incidence of *Staphylococcus* spp. in 20 included studies.

Author, year	Cases (N)	Causative organism, N (%)			(Refs.)
		CoNS	<i>S. aureus</i>	Others ^a	
Knee and hip					
Phillips <i>et al</i> , 2006	75	27 (36.0)	22 (29.3)	26 (34.7)	(2)
Moran <i>et al</i> , 2007	112	47 (42.0)	53 (47.3)	12 (10.7)	(27)
Teterycz <i>et al</i> , 2010	82	39 (47.6)	43 (52.4)	0 (0.0)	(19)
Tsai <i>et al</i> , 2015	144	24 (16.7)	43 (29.9)	77 (53.5)	(13)
Kuiper <i>et al</i> , 2013	91	13 (14.3)	50 (54.9)	28 (30.8)	(20)
Knee					
Wilde <i>et al</i> , 1988	15	10 (66.7)	0 (0.0)	5 (33.3)	(39)
Burger <i>et al</i> , 1991	39	13 (33.3)	19 (48.7)	7 (17.9)	(38)
Ip <i>et al</i> , 2005	14	1 (7.1)	6 (42.9)	7 (50.0)	(28)
Fulkerson <i>et al</i> , 2006	84 ^b	30 (35.7)	27 (32.1)	27 (32.1)	(12)
Sharma <i>et al</i> , 2008	108 ^b	28 (25.9)	26 (24.1)	54 (50.0)	(6)
Stefansdottir <i>et al</i> , 2009	426	131 (30.8)	134 (31.5)	161 (37.8)	(1)
Nickinson <i>et al</i> , 2010	121	59 (48.8)	16 (13.2)	46 (38.0)	(8)
Bjerke-Kroll <i>et al</i> , 2014	390	76 (19.5)	77 (19.7)	237 (60.8)	(44)
Holmberg <i>et al</i> , 2015	145	33 (22.8)	53 (36.6)	59 (40.7)	(40)
Matsumoto <i>et al</i> , 2015	50	10 (20.0)	25 (50.0)	15 (30.0)	(33)
Total	1,392	391 (28.1)	383 (27.5)	618 (44.4)	
Hip					
Giulieri <i>et al</i> , 2004	63	11 (17.5)	27 (42.9)	25 (39.7)	(42)
Ip <i>et al</i> , 2005	22	3 (13.6)	6 (27.3)	13 (59.1)	(28)
Fulkerson <i>et al</i> , 2006	110 ^b	31 (28.2)	40 (36.4)	39 (35.5)	(12)
Rafiq <i>et al</i> , 2006	255	171 (67.1)	33 (12.9)	51 (20.0)	(9)
Sharma <i>et al</i> , 2008	140 ^b	50 (35.7)	27 (19.3)	63 (45.0)	(6)
Lutro <i>et al</i> , 2014	278	113 (40.6)	53 (19.1)	112 (40.3)	(32)
Ibrahim <i>et al</i> , 2014	125	35 (28.0)	49 (39.2)	41 (32.8)	(41)
Bjerke-Kroll <i>et al</i> , 2014	395	77 (19.5)	102 (25.8)	216 (54.7)	(44)
Triantafyllopoulos <i>et al</i> , 2015	60	11 (18.3)	31 (51.7)	18 (30.0)	(43)
Total	1,448	502 (34.7)	368 (25.4)	578 (39.9)	
Total	3,344	1,043 (31.2)	962 (28.8)	1,339 (40.0)	

^aIncluding *Streptococci* spp., *Enterococci* spp., Diphtheroids, *Escherichia coli*, *Pseudomonas* spp., *Acinetobacter* spp. and negative cultures.

^bCases were positive specimens isolated from knee or hip. CoNS, coagulase-negative staphylococci; *S. aureus*, *Staphylococcus aureus*.

no significant changes in susceptibility patterns from the years 1993 to 2007, in Norway. Although there were some regional differences (32), the changes in susceptibility patterns of CoNS may have a contribution to the result that CoNS were more commonly observed in the hip than the knee in the present review.

CoNS were the prevalent pathogen in early phase PJI, whereas *S. aureus* occurred predominantly in the late phase. Previous reports have demonstrated that contamination in the operating room and haematogenous dissemination through sepsis or transient bacteremia were the two primary routes of infection following joint replacement (17,18,45). Early and delayed PJI were likely to be caused by intraoperative contamination, whereas the most common source of late infection was haematogenous spread (25,26,49).

In order to reduce intraoperative contamination risk, antibiotic prophylaxis has been routinely applied in clinical practice in addition to applying physical measures (7). However, among 131 *Staphylococcus*-positive specimens, Sharma *et al* (6) indicated that 6 of the 53 *S. aureus* isolates were methicillin-resistant and all MSSA isolates were cephalothin- and cefazolin-sensitive, whereas 65% of the CoNS isolates were resistant to cephalothin. Similarly, Nickinson *et al* (8) concluded that almost all antibiotics were more effective against *S. aureus* when compared with CoNS.

For another, Teterycz *et al* (19) reported that bacteremia was detected in MRSA and MSSA in 163 episodes and not in CoNS infections. Other researchers have identified a similar phenomenon (11). All these studies indicated that *S. aureus* were more virulent and exhibited a shorter incubation

Table III. Distribution characteristics of *Staphylococcus* spp. in different phases of periprosthetic joint infection.

Organisms	Early (0 to 3 months)			Delayed (3 to 24 months)			Late (>24 months)			Overall, N (%)
	N	% of organisms	% of phase	N	% of organisms	% of phase	N	% of organisms	% of phase	
CoNS	56	37.6	36.6	62	41.6	28.6	31	20.8	20.1	149 (28.4)
<i>S. aureus</i>	32	20.5	20.9	65	41.7	30.0	59	37.8	38.3	156 (29.8)
Others ^a	65	29.7	42.5	90	41.1	41.5	64	29.2	41.6	219 (41.8)
Total	153	29.2		217	41.4		154	29.4		524 (100.0)

^aIncluding *Streptococci* spp., *Enterococci* spp., *Diphtheroids*, *Escherichia coli*, *Pseudomonas* spp., *Acinetobacter* spp. and negative cultures.

time (19), greater ability to form biofilms and were able to adapt locally (50) when compared with CoNS (23,28).

Consequently, *S. aureus* relatively rarely caused infections in the early phase following surgery due to the comprehensive perioperative protocol (51). However, with the subsiding of precaution in the late phase, for example the decrease of antibiotic concentration from antibiotic-loaded cement (52,53), *S. aureus* may rapidly cause infections.

Additionally, biofilm formation has been demonstrated as a mechanism in establishing antibiotic resistance (16,28,54,55). *S. aureus* were frequently associated with acute clinical presentation produced by numerous intra-articular planktonic pathogens (25,54,55) and were indicated to be the most frequent microbe that produces a biofilm (54), suggesting that *S. aureus* may be detected and treated in the early phase. However, the biofilms developed by CoNS, particularly *S. epidermidis*, have often exhibited negative results on blood bacterial culture and have only been identified after the removal and culture of the implant (23). Therefore, CoNS may have invaded the implant and caused PJI in the early phase, prior to any noticeable symptoms of PJI. Taking this into account, we hypothesized that these factors may explain why CoNS were more common in the early phase of PJI and *S. aureus* were more common in the late phase of PJI.

MSSA comprised up to 70% of all *S. aureus* in PJI. According to the present findings and the reports of other studies (15,32,34,56), the isolated rate of MSSA in PJI is much higher than that of MRSA. However, MRSA has been indicated to be more resistant to antibiotics (57) and has a worse patient prognosis than MSSA (19,34,35). Lora-Tamayo *et al* (34) demonstrated that 88% of MRSA-PJI treatment failure occurred during the early stage of treatment; whereas 50% of MSSA-PJI treatment failure occurred following cessation of therapy. Alternatively, Liu *et al* (57) showed that MSSA harbored more diverse and abundant virulence factor genes than MRSA. Due to offsetting the costs associated with virulence and methicillin resistance (57,58), the toxin expression may decrease in MRSA (57). This implied that MSSA was more virulent than MRSA. Furthermore, the hematogenous PJI was indicated to be caused by MSSA in 88% of episodes (34) and the late phase of PJI was thought to be the result of hematogenous spread (25,26,49). This may explain why hematogenous PJI or late phase PJI always developed suddenly and progressed rapidly.

From previous implantation to arthroplasty infection onset, the median time delay of MRSA and MSSA was 16 and 361 days, respectively, as Teterycz *et al* (19) described. In a joint registry review, Siddiqui *et al* (59) also clearly indicated that 44% of early infections following primary TKA were the result of MRSA. Therefore, when combined with the findings of the present review, *S. aureus* occurred predominantly in the delayed and late phases of PJI, and MSSA was in the majority. Therefore, we had reason to conclude that MRSA may be the predominant bacteria retrieved in the early phase, and MSSA in the delayed and late phases of PJI caused by *S. aureus*.

5. Agreement and disagreement with other studies

Consistent with previous studies (2,6,8,9,17,23,25,29,39,60), the most frequently encountered isolates in the present review

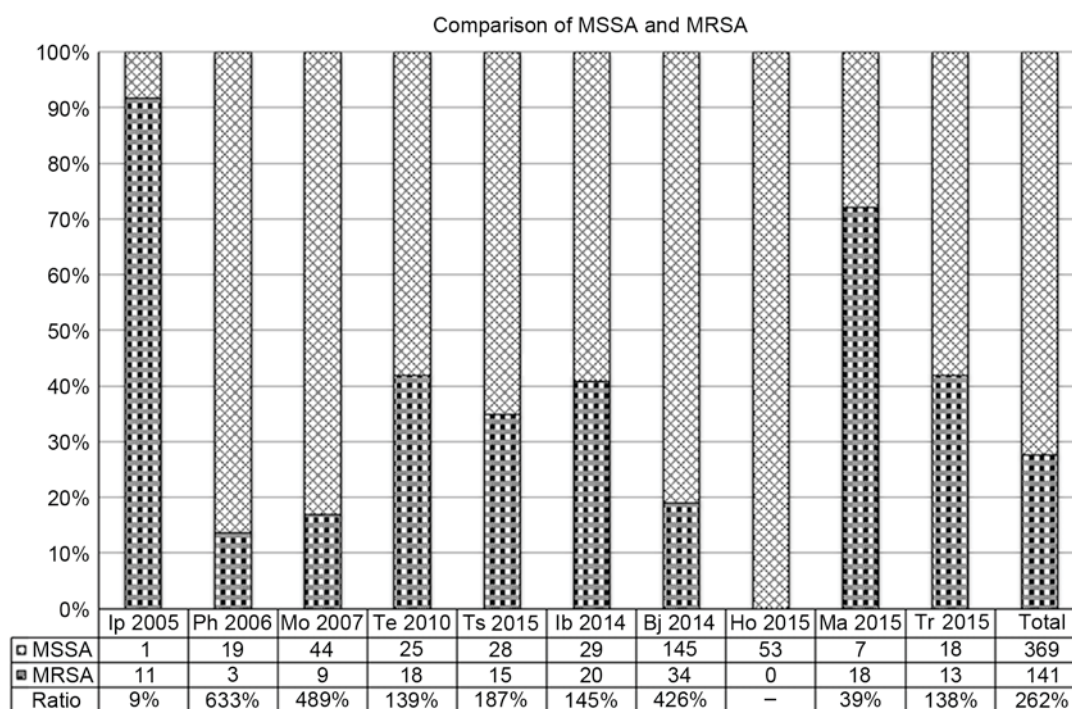


Figure 2. Comparison of MSSA and MRSA in 10 included studies. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; Ip, Ip *et al* (28); Ph, Phillips *et al* (2); Mo, Moran *et al* (27); Te, Teterycz *et al* (19); Ts, Tsai *et al* (13); Ib, Ibrahim *et al* (41); Bj, Bjerke-Kroll *et al* (44); Ho, Holmber *et al* (40); Ma, Matsumoto *et al* (33); Tr, Triantafyllopoulos *et al* (43).

were CoNS, followed by *S. aureus*. Although multiple studies have been conducted (1,12,27,28,31,41,61) revealing that PJI was predominantly caused by *S. aureus* when compared with CoNS, the overall proportions were similar in the majority of these studies. The slight disparity may be due to the differences of infection control policies in different regions or hospitals (24,32,62).

Findings of the present review revealed the distribution characteristics of CoNS and *S. aureus* in hip and knee arthroplasties were in broad agreement with previously published data (1,8,9,32,41,60). However, the present review did not further discuss the feature modifications of *Staphylococcus* spp. in PJI longitudinally due to lack of sufficient data. As previously reported, the incidences of CoNS and *S. aureus* reversed over time in hip and knee arthroplasties (8,9,17). For example, Muilwijk *et al* (17) and Rafiq *et al* (9) demonstrated that *S. aureus* appeared to become more prevalent following hip arthroplasties, with CoNS decreasing in prevalence, which was reversed in the infected knee replacements (8). However, in 2014, Aggarwal *et al* (62) and Bjerke-Kroll *et al* (44) demonstrated that there were no significant differences in CoNS and *S. aureus* when comparing hip to knee arthroplasties. Only patients who underwent two-stage revision were included in the study conducted by Bjerke-Kroll *et al* (44), which may lead to a degree of bias in predicting the overall distribution characteristics of *Staphylococcus* spp. in hip and knee cases.

In different phases of PJI, the present review indicated that the delayed phase of infection (41.4%) was the most common infection, followed by late phase (29.4%) and early phase (29.2%) infection. This result was associated with the PJI classification system. Phillips *et al* (2) revealed that 36% of patients

exhibited late phase PJI and 35% exhibited delayed phase PJI, when PJI occurred greater than one year after surgery were classified as late infections. However, of all the infections, 52% arose between 3 months and 2 years (delayed phase) and 19% after 2 years (late phase), when the classification system applied in our review was used (2).

Ascione *et al* (31) indicated that in 159 patients with early or delayed PJI, *S. aureus* (39%) was the principal cause of early infections, followed by CoNS (13%), using the same classification system for PJI that was chosen in the present review. This study disagreed with the findings of the present review. Under similar conditions, the results of the present review did not agree with Zimmerli *et al* (26), who proposed that the early phase PJI were typically caused by virulent bacteria, whereas delayed phase PJI were commonly caused by less virulent pathogens. As described earlier, subclinical syndrome always occurred at the beginning of the PJI caused by CoNS, which may make it difficult to diagnose during the early (27). Therefore, the correct diagnosis may be delayed if the clinical manifestations alone are depended upon, which may result in certain differences in various studies. This suggests that more rigorous methods are required for the early diagnosis of PJI (27,63). Even though the classification system used in the present review is universally used (2,25), specific disadvantages of this classification system are apparent. In particular, Sendi *et al* (11) stated that this classification system was not optimal for distinguishing exogenous and haematogenous PJI, when PJI was caused by *S. aureus* <2 years after surgery.

In a large retrospective and multicenter study of PJI caused by *S. aureus*, 77% of cases were caused by MSSA and 23% of episodes were caused by MRSA among a total of 345 episodes (34). In 2007, Salgado *et al* (15) also revealed that

24% of cases were the result of MSSA and 9% of cases were a result of MRSA in THA or TKA PJI. These were similar to the findings of the present review. But perhaps because MRSA typically results in a worse prognosis than MSSA and predominantly occurred in the early phase of PJI, various studies (15,59,64) have investigated MRSA-PJI, whereas little is known regarding MSSA-PJI at present. Therefore, the present review indicated that MRSA occurred primarily in the early phase of PJI and MSSA occurred predominantly in the delayed and late phases of PJI, which may aid the understanding of the distribution characteristics of these two strains in PJI and aid the development of reasonable antibiotic treatment strategies.

6. Antibiotic treatment

Deficiencies in the current antibiotic-resistant bacteria treatment strategy. In 2010, Teterycz *et al* (19) demonstrated that MRSA had the worst outcome in arthroplasty infections, which was cured in 39% of episodes, compared with 60% of MSSA episodes and 77% of CoNS episodes. Therefore, multiple prevention and treatment measures have been primarily used to treat *S. aureus* (or MRSA) in clinical practice (56), rather than CoNS. However, in the present review, 31.2% of PJI cases were indicated to be caused by CoNS. Furthermore, MRSE isolated from PJI has become an increasingly popular pathogen over the past decades. For example, James *et al* (30) revealed that a quarter of patients had MRSE on their skin prior to hip arthroplasties and 18/30 cultures of *S. epidermidis* were isolated, of which 12 were positive for MRSE in 1994. Moran *et al* (27) indicated in their retrospective review of 112 patients that 60% of CoNS cases (47% of patients) were methicillin-resistant and 88% of CoNS cases were penicillin-resistant. The changes in the distribution characteristics of pathogens in PJI emphasized the requirement of choice for appropriate treatment protocols.

Choice of antibiotic treatment. Although multiple factors must be considered prior to deciding on an antibiotic treatment strategy, the most critical factors are the bacterial species and the phases of PJI.

The feature of pathogens has been suggested to be a strong indicator of the outcome of antibiotic treatment (3,28,62). Joshy *et al* (65) indicated that PJI caused by MRSA or MRSE, following TKA, exhibited significantly lower satisfactory outcomes (18 and 67%, respectively) when compared to those caused by MSSA. To prevent these refractory infections, we suggest that prophylactic antibiotics should include vancomycin and gentamicin, a theory supported by Sharma *et al* (6). In their clinical study, all Gram-positive bacteria, such as *S. epidermidis* and *S. aureus* (12), were vancomycin-sensitive and almost all Gram-negative organisms were gentamicin-sensitive in 248 isolates from revision hip and knee arthroplasties (6).

Unfortunately, various studies have revealed that although CoNS and MRSA infections decreased after patients received vancomycin prophylaxis (14), MSSA infections were more likely to be developed. Similarly, MRSA infections were more common if patients received cefazolin prophylaxis alone (7,14). This phenomenon may be due to reduced antimicrobial spectrum and decreased efficacy of vancomycin as compared to cefazolin

for CoNS and *S. aureus* (14). Therefore, for staphylococcal PJI cases, the combined application of antibiotics was recommended to improve the therapeutic effect (66), prevent the occurrence of antibiotic resistance and reduce systemic toxicity (67,68).

With the emergence of vancomycin-resistant *Enterococcus* spp. (69), there was an urgent requirement to take a number of effective measures to slow the progression of antibiotic-resistant strains. Therefore, a number of medical researchers recommended that vancomycin should only be administered to patients possessing a known drug-resistant bacteria carrier status (7,28) with the exception of the combined application of antibiotics. Additionally, various studies had demonstrated that early screening of MRSA (56,64) and MRSE (46) may significantly reduce the incidence of these resistant strains in PJI, thus screening for MRSA and MRSE in patients prior to surgery was necessary to establish a suitable antibiotic prophylaxis and treatment policy.

The empiric antibiotic therapy should be guided by the phases of PJI until the correct culture results are available (12,37). In the present review, MRSA and CoNS were the prevalent genus identified in the early and delayed phase of PJI and the infections were treated with vancomycin and surgical debridement, which have been recommended by other studies (1,10,12). In late phase PJI, the majority of PJI cases were the result of hematogenous seeding by MSSA. For infections in this phase, Fulkerson *et al* (12) have suggested combination therapy with cefazolin and gentamicin, whereas Lora-Tamayo *et al* (34) recommended the combination of quinolones plus rifampin. However, regardless of the phase of PJI, resistant pathogens, such as MRSA and MRSE, typically exhibit a high rate of treatment failure (70), particularly in the delayed and late phase PJI. Hence, in certain studies, revision (one-stage or two-stage) coupled with systemic antibiotics was often necessary (8,10,41,65). When confronted with incurable PJI, arthrodesis, resection arthroplasty and amputation (65) may have to be adopted for survival. The sensitivity of the causative organisms towards antibiotics was the basis of PJI treatment.

7. Limitations

The present review exhibited several limitations. The sample size used may be too small for the effective classification of PJI and *S. aureus*; therefore, the present results, in conjunction with conclusions from alternative studies, were analyzed carefully in order to attain a reliable conclusion. Furthermore, the present review analyzed exclusively staphylococcal infections due to CoNS and *S. aureus* and did not factor in alternative pathogens that were categorized as 'Others'. Hence, the present conclusion was unserviceable for PJI caused by other pathogens. Additionally, a small fraction of polymicrobial infection in some included studies was integrated into the monomicrobial PJI for analyzing the frequency of sole pathogens. Due to the limited information of mixed infections, we were unable to determine the characteristic of polymicrobial infection in PJI.

8. Conclusions

PJI is a serious clinical problem for patients and doctors. In the present systematic review, the pooled rates of CoNS and *S. aureus* accounted for 60.0% of the isolated organisms in 20

included studies. CoNS were identified to be a more common cause of PJI than *S. aureus*, particularly in the cases of hip PJI. In different phases of PJI, CoNS were the prevalent genus in the early phase, whereas *S. aureus* was primarily observed in the late phase, although CoNS and *S. aureus* were exhibited in a similar proportion in the delayed phase. In PJI caused by *S. aureus*, MSSA occurred more frequently. Moreover, MRSA occurred predominantly in the early phase, whereas MSSA was more common in the delayed and late phases.

To prevent PJI, the combined application of antibiotics and comprehensive early carrier status screening of MRSA and MRSE are recommended. In terms of antibiotic treatment, vancomycin and gentamicin should be included in prophylactic antibiotics in order to cover Gram-positive and Gram-negative organisms. Vancomycin and surgical debridement were often used in the early and delayed phase of PJI and the combination of cefazolin and gentamicin or the combination of quinolones and rifampin were proposed in the late phase, prior to the final culture results. Although there are limitations in this review, our results may be useful for clinical practice and further scientific research of PJI.

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