‘Early’ Prosthetic Joint Infections following Total Knee Arthroplasty are More Resistant and Polymicrobial than ‘Late’ Prosthetic Joint Infections: Antibiotic Sensitivities to Guide Empiric Antibiotic Choice

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INTRODUCTION:
Prosthetic joint infection (PJI) is the leading cause of revisions following total knee arthroplasty (TKA). As the microorganism profile may not be available on initial PJI presentation, empiric antibiotics are guided by the most likely causative organisms. We propose categorising PJIs based on implant age, where early infections are less than a year since the primary arthroplasty and late infections are greater than a year. The aim of this study is to 1) compare the microorganism and resistance profile in early and late PJIs, using Fulkerson modification of Tsukayama infection criteria and proposed Auckland criteria; 2) recommend appropriate empiric antibiotics.
METHODS:
A multicentre retrospective review was performed over a 15-year period. Each first episode PJIs were categorised according to both Fulkerson modification of Tsukayama criteria ('Class A' (early post-operative PJIs <4 weeks), 'Class B' (chronic PJIs >4 weeks) or 'Class C' (haematogenous PJIs >4 weeks)) and proposed Auckland criteria ('early' (<1 year) or 'late' (>1 year)). Then each case was classified into monomicrobial or polymicrobial infection. For each positive culture, the causative organism, Gram-stain and antibiotic sensitivity were recorded.
RESULTS:
Of eligible patients, 232 culture-positive PJI cases were included.. When using the Tsukayama infection criteria, the most common organism in Class A (36%) and Class B (28%) PJIs was coagulase negative *Staphylococcus* (CONS). In Class C PJIs, *Staphylococcus aureus* (*S. aureus*) was the most common (41%). Organisms causing Class A infections were significantly more likely to be resistant and polymicrobial than Class B or Class C infections (Table 1). The predominant organisms in 'Early (<1 year) PJIs were CONS (29%), while *S. aureus* and *Streptococci* species (36%) were the most common in late (>1 year) PJIs. A significantly higher proportion of polymicrobial cases (31% vs 4%; P<0.00001) and resistant organisms (35% vs 6%, P<0.0002) were reported in the early infections. The distribution of Gram-negative cases was similar between early and late infections (19% vs 11%; P=0.1143) (Table 2).

The proportion of patients in Tsukayama Class-A infection who would have been adequately treated with penicillin and flucloxacillin monotherapy is 5% and 26%, respectively. Vancomycin monotherapy would have covered 75% of the cases. Vancomycin with the addition of a Gram-negative antibiotic showed a higher coverage of above 80% (Table 3). In Class-B and C infections, vancomycin monotherapy showed a high coverage of 80% and 94%, respectively (Table 3).

When using the Auckland Classification, early infections were highly resistant against penicillin and flucloxacillin monotherapy, but 82% of the cases were covered by vancomycin alone. In contrast, flucloxacillin or cephazolin alone covered 84% of the late cases (Table 3).

Based on the antibiotic coverage for PJI cases in Table 3, we have recommended antibiotic regime for non-septic and septic patients in each infection classification (Table 4). For non-septic patients, we aimed for antibiotic coverage greater 80% and for septic patients the cut-off was 90%. We recommend vancomycin monotherapy for early non-septic PJIs with the addition of a Gram-negative cover in septic patients, preferably gentamicin, as the combination showed the highest coverage of 91%. In late infections, we recommend flucloxacillin or cephazolin for early infections. For septic late infections, dual therapy with any of the three Gram-negative agents is recommended.
DISCUSSION AND CONCLUSION:
Based on the microbiological pattern in Tsukayama criteria, vancomycin with the consideration of Gram-negative agent should be considered for Class-A infections given the high proportion of resistant and polymicrobial cases. For Class-C infections cephazolin or flucloxacillin may provide sufficient cover for non-resistant Gram-positives and we recommend antibiotics to be withheld in Class-B infections until cultures and sensitivities are known.

*This study has been accepted for publication in the Journal of Arthroplasty

Table 1. Tsukayama Classification of PJIs

	A[a]	B[b]	C[c]	P values
Time cut-off	Post op (<6 weeks)	Chronic (>6 weeks)	Hematogenous (>6weeks)	-
Cases	27% (63/232)	25% (57/232)	48% (112/232)	-
% (n=232)				
Discrete number of organisms (n=303)	38% (115/303)	22% (67/303)	40% (121/303)	-
Polymicrobial cases	51%	11%	4%	A vs B < 0002
% (n=232)	(32/63)	(6/57)	(4/112)	B vs C 0.09
				A vs C <.00001
Cases involving at least one Gram-negative organism % (n=232)	25% (16/63)	21% (12/57)	6% (7/112)	A vs B = 0.57
				B vs C = 0.004
				A vs C = 0.0003
Resistant cases	50%	20%	6%	A vs B = 0.0009
% (n=232)	(31/62)	(11/54)	(5/112)	B vs C = 0.0011
				A vs C < 0002
Most common organism	CoNS[d]	CoNS[d]	*S. aureus*	-
	36% (41/115)	28% (19/67)	41% (50/121)	

[a]Class A=infection occurring within 4 weeks since primary total knee orthoplasty; [b]Class B=infection occurring after 4 weeks from primary total knee orthoplasty; [c]Class C=same organisms isolated from PJI and remote site of infection OR patient presents with acute systemic signs of infection (fever, rigors, night sweats) and/or local signs of infection (acute joint inflammation, rapid onset of pain) after 4 weeks since primary total knee orthoplasty; [d]Coagulase negative *Staphylococcus aureus*; [e]*Staphylococcus aureus*

Table 2. Auckland Classification of PJIs

	Early[a]	Late[b]	P values
Time cut-off	<1 year	>1 year	-
Cases	53%	47%	-
% (n=232)	(124/232)	(108/232)	
Discrete number of organisms (n=303)	60% (183/303)	40% (120/303)	-
Polymicrobial cases	31%	4%	<.00001
% (n=232)	(38/124)	(4/108)	
Cases involving at least one Gram-negative organism % (n=232)	19% (23/124)	11% (12/108)	0.11
Resistant cases	35%	6%	<.0002
% (n=232)	(42/121)	(6/107)	
Most common organism	CoNS[c]	*Streptococci*	-
	29% (53/183)	*S. aureus*[d] 36% (43/120)	

[a]Early prosthetic joint infections=infections occurring within a year since primary total knee orthoplasty; [b]Late prosthetic joint infection=infections occurring after a year since primary total knee orthoplasty; [c]Coagulase negative *Staphylococcus aureus*; [d]*Staphylococcus aureus*

Table 3. Most common causative microorganism in different classification system and the predicted successful antibiotic coverage rate

		Auckland Classification		**Tsukayama Classification**		
		Early	Late	A	B	C
Polymicrobial infections (%)		31%	4%	51%	11%	4%
Causative organisms (%)		CONS[a] (29%) *S. aureus*[b] (25%) Gram-negatives (17%) *Streptococci* (11%)	*S. aureus*[b] (36%) *Streptococci* (36%) CONS[a] (15%) Gram-negatives (10%)	CONS[a] (36%) Gram-negatives (21%) *S. aureus*[b] (19%) *Enterococci* (13%)	CONS[a] (28%) *S. aureus*[b] (24%) *Streptococci* (19%) Gram-negatives (18%)	*S. aureus*[b] (41%) *Streptococci* (40%) CONS[a] (9%) Gram-negatives (0%)
Percentage of patients who would be on adequate antibiotic regime						
Monotherapy	Penicillin monotherapy	20% (24/120)	46% (49/107)	5% (3/61)	27% (15/55)	50% (55/111)
	Flucloxacillin monotherapy	46% (55/118)	84% (89/106)	26% (16/61)	57% (30/53)	89% (98/110)
	Vancomycin monotherapy	82% (101/123)	89% (96/108)	75% (47/63)	80% (45/56)	94% (105/112)
Dualtherapy	Vancomycin + gentamicin	91% (20/22)	91% (10/11)	88% (15/17)	100% (9/9)	86% (6/7)
	Vancomycin + ciprofloxacin	85% (17/19)	90% (9/10)	93% (14/15)	67% (6/8)	100% (6/6)
	Vancomycin + ceftazidime	84% (16/19)	100% (11/11)	80% (12/15)	100% (8/8)	100% (7/7)

[a]Coagulase negative *Staphylococcus aureus*; [b]*Staphylococcus aureus*

Table 4. Recommended antibiotic regime for each prosthetic joint infection classification criteria

	Auckland Classification		**Tsukayama Classification**		
	Early	Late	A	B	C
Not septic	Vancomycin	Flucloxacillin/cefuroxim	Vancomycin + Gram-negative cover	Withhold antibiotics until cultures	Flucloxacillin/cefuroxim
Septic	Vancomycin + Gram-negative cover	Flucloxacillin/cefuroxim + Gram-negative cover	Vancomycin + Gram-negative cover	Vancomycin + Gram-negative cover	Flucloxacillin/cefuroxim + Gram-negative cover