

# Implications of the changing pattern of bacterial infections following total joint replacements

D Ip, SK Yam, CK Chen

Department of Orthopaedics and Traumatology, Pamela Youde Nethersole Eastern Hospital, Hong Kong

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## ABSTRACT

**Purpose.** To retrospectively review the causative organisms isolated from infected hip and knee replacements requiring revision.

**Methods.** We reviewed a consecutive series of 36 patients who underwent revision hip or knee arthroplasties due to bacterial infection at Pamela Youde Nethersole Eastern Hospital in Hong Kong between 1995 and 2003. The male to female ratio was 1:2, and the mean age of patients was 70 years (range, 54–82 years). The mean duration of follow-up was 3.8 years (range, 1.1–8.3 years). No patient was lost to follow-up. All 14 revision knee patients had previously undergone cemented and patella-resurfacing total knee arthroplasties. Of the 22 revision hip patients, 9 had cementless, 6 had cemented, and 7 had hybrid total hip arthroplasties previously.

**Results.** None of the bacteria isolated from 1995 to 1996 were multiple-drug resistant. Subsequently, however, most of the isolates were multiple-drug resistant, with methicillin-resistant *Staphylococcus aureus* (MRSA) being the most common. Half of the isolates of *Staphylococcus epidermidis* and *Escherichia coli*

demonstrated multiple-drug resistance. The incidence of positive culture in revision hip patients was 59%, 46% of which were MRSA. All 13 revision hips with positive cultures showed chronic sepsis: 4 occurred within one year and 10 occurred 2 or more years after the index arthroplasty. The incidence of positive culture in revision knee patients was 57%, 46% of which were MRSA. All 8 revision knees with positive cultures showed chronic sepsis: 3 occurred within one year, 5 occurred 2 or more years after the index arthroplasty. Only one patient, who was infected with gram-negative bacilli, required a second revision for residual sepsis. Harris hip scores for the revision hip patients improved from a mean of 65 (range, 55–75) to 85 (range, 75–90). Knee Society knee scores of the revision knee patients improved from a mean of 68 (range, 55–75) to 80 (range, 70–85). There were no radiological signs suggestive of loosening in the 2 groups at the latest follow-up.

**Conclusion.** This study found a definite increase in multiple-drug-resistant bacteria isolated from periprosthetic infections around total hip and knee prostheses.

**Key words:** arthroplasty, replacement; bacterial infections; postoperative complications

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## INTRODUCTION

There is a paucity of reports in the literature on bacterial infections after total joint replacements. The nature of the causative bacteria affects the management of patients, the nature and duration of antibiotic administration, and the prognosis of reconstruction efforts. It is imperative to periodically review the bacteriology involved, to identify any changing patterns over time, and to analyse the epidemiological surveillance data locally, nationally, and between different countries.

Advances in bacteriology, pharmacology, molecular biology, and genetics have helped clinicians comprehend the causes of the often rapid acquisition of multiple-drug-resistant bacteria, notably *Staphylococcus aureus*, *Staphylococcus epidermidis*, and some gram-negative bacilli. Epidemiological surveillance studies continue to provide clinicians with valuable data on patterns of bacterial drug resistance. Coupled with comparative studies of community strains as opposed to nosocomial clones or strains, surveillance data can help physicians to understand the best way to manage infections around total joint implants by these fastidious organisms. As shown in this study, the incidence of multiple-drug-resistant bacteria isolated from periprosthetic infections around total hip and knee prostheses is increasing.

## MATERIALS AND METHODS

We retrospectively reviewed a consecutive series of 36 patients who underwent revision hip (n=22) or knee (n=14) arthroplasties for bacterial infection in the Pamela Youde Nethersole Eastern Hospital, Hong Kong, between 1995 and 2003. Infections were either acute (within 4 weeks<sup>1</sup>) deep sepsis or delayed septic loosening after total hip or knee replacement. The male to female ratio was 1:2, and the mean age of patients was 70 years (range, 54–82 years). The mean duration of follow-up was 3.8 years (range, 1.1–8.3 years). No patient was lost to follow-up. All 14 revision knee patients had previously undergone cemented and patella-resurfacing total knee arthroplasties. Of the 22 revision hip patients, 9 had cementless, 6 had cemented, and 7 had hybrid total hip arthroplasties previously. The overall numbers of total hip and total knee arthroplasties in our hospital were 533 and 830, respectively, during the same study period. 30 of the patients had their index arthroplasties performed in our hospital. Characteristics of the 36 infected patients are shown in the Table.

Preoperative assessment included serial

radiographs, white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and joint aspirations. Tissues acquired during surgery were sent for frozen section and bacterial cultures in all cases, regardless of the results of preoperative workups for sepsis. Frozen section samples were taken from the joint pseudocapsule, membranes, or tissues at the bone-prosthesis interface, or from any other suspicious areas. Multiple intra-operative cultures were then taken from areas where samples of frozen section were harvested. More than 5 polymorphonuclear leukocytes per high-power field in the frozen section specimen were indicative of infection. Cultures were incubated in aerobic and anaerobic environments, as well as acid-fast cultures. Aerobic blood-agar plates were incubated in air, the chocolate agar plates in 10% carbon dioxide, and anaerobic plates in the anaerobic chamber. The aerobic and anaerobic plates and enrichment broths were incubated for 5 days. Extra-long incubation periods of up to 7 to 10 days were sometimes used to help pick up small-colony variants in subjects who may have received antibiotics preoperatively. Lowenstein-Jensen medium and mycobacterium growth indicator tubes were used to culture acid-fast bacilli. Gram staining was performed for every patient.

A positive intra-operative culture was a definite diagnosis of infection. Isolates were considered significant if they grew on direct plating, or if an indistinguishably similar strain grew on enrichment in more than one culture.

Organisms were considered contaminants if distinguishable strains were isolated from enrichment broths, and no growth occurred with direct plating. A single isolate of a strain from only one enrichment culture was not considered significant.

Two-stage reconstruction was used for all revision total joint arthroplasties. Vancomycin-loaded cement (dosage, 2 g) was used when there was a positive culture of methicillin-resistant *Staphylococcus aureus* (MRSA), when the patient had been an MRSA carrier, or when there was a mini-outbreak in the ward with no positive cultures obtained. Tobramycin was added to the cement (dosage, 1 g tobramycin in 40 g of cement powder) during the second-stage revision in other situations. Other antibiotics such as gentamicin and cephalosporins were not used by our unit. Intravenous antibiotics were uniformly given between the 2 stages of reconstruction for 6 weeks, but not afterwards.

Clinical and radiological results of all patients were evaluated. Serial Harris hip scores and serial Knee Society knee scores were measured. Serial radiological assessment of the knee was charted according to the

guidelines of the Knee Society.<sup>2</sup> The quality of cementation of the hip was charted according to the O'Neill and Harris system<sup>3</sup>; while the cementless hips were monitored for signs of osseous integration such as the presence of spot welds, or signs of instability such as the presence of pedestals, the shedding of beads, or changes in alignment.

## RESULTS

Intra-operative culture was the gold standard for diagnosing infection. From 1995 to 1996, none of the bacteria isolated were multiple-drug

resistant. Subsequently, however, most of the isolates were multiple-drug resistant, with MRSA being the most common. Half of the isolates of *S epidermidis* and *Escherichia coli* demonstrated multiple-drug resistance.

In revision hip patients, the incidence of positive culture was 59%, 46% of which were MRSA. All 13 revision hips with positive cultures showed chronic sepsis: 4 occurred within one year of the index arthroplasty, while the others occurred 2 or more years after the index operation. In revision knee patients, the incidence of positive culture was 57%, 46% of which were MRSA. All 8 revision knees with positive cultures showed chronic sepsis, 3 occurred within one year of

**Table**  
**Patient characteristics (n=36)**

Patient No.	Age (years)	Sex	Diagnosis <sup>†</sup>	Site of surgery	Prosthesis durability (months)	Revision year	Organism isolated <sup>‡</sup>
1	67	M	OA	Right knee	24	1995	<i>S epidermidis</i>
2	79	F	OA	Right hip	36	1995	Not isolated
3	80	M	OA	Left knee	19	1996	MSSA
4	72	M	OA	Right hip	34	1996	<i>S epidermidis</i>
5	75	M	OA	Left hip	11	1997	MRSA
6	65	M	OA	Left hip	20	1997	MRSA
7	64	F	OA	Right hip	28	1997	Not isolated
8	63	F	OA	Left hip	35	1997	<i>S epidermidis</i>
9*	73	F	OA	Left knee	60	1998	Not isolated
10	73	F	OA	Left hip	4	1998	MRSA
11	54	M	AVN	Right hip	28	1998	MRSA
12	77	F	OA	Left hip	9	1999	Not isolated
13	73	F	OA	Left knee	11	1999	MRSA
14	77	F	OA	Left knee	38	1999	Not isolated
15*	65	F	AVN	Right hip	37	1999	Not isolated
16	62	F	OA	Left hip	35	2000	Not isolated
17	59	F	OA	Left knee	20	2000	MRSA
18	72	M	OA	Right hip	26	2000	MRSA
19	71	F	OA	Right hip	50	2000	Not isolated
20	63	F	OA	Left knee	35	2000	Not isolated
21*	67	F	OA	Left hip	65	2001	<i>E coli</i>
22	79	F	OA	Right hip	48	2001	Not isolated
23	75	F	OA	Right hip	50	2001	Not isolated
24*	82	F	OA	Left hip	23	2001	Bacteroides
25	73	F	OA	Left hip	6	2001	MRSA
26	72	F	OA	Right hip	26	2001	Not isolated
27	54	F	OA	Right knee	6	2002	MRSA
28*	82	F	OA	Left knee	23	2002	Not isolated
29	63	M	OA	Left hip	17	2002	<i>E coli</i>
30	78	F	OA	Right knee	28	2002	<i>E coli</i>
31	71	M	OA	Left knee	11	2002	MRSA
32	66	M	OA	Left hip	22	2003	<i>S epidermidis</i>
33	64	F	OA	Right knee	28	2003	Not isolated
34	63	F	OA	Left hip	35	2003	<i>E coli</i>
35*	77	M	OA	Left knee	60	2003	Not isolated
36	74	M	OA	Left knee	14	2003	MRSA

\* Patients underwent index operation in other hospitals

† OA denotes osteoarthritis and AVN avascular necrosis

‡ MSSA denotes methicillin-susceptible *Staphylococcus aureus* and MRSA methicillin-resistant *Staphylococcus aureus*

the index operation, while the remaining 5 occurred 2 or more years after the index operation. There was no acute (before postoperative 4 weeks) sepsis in the 2 groups. Only one patient, infected with gram-negative bacilli, required a second revision for residual sepsis.

The mean period from index operation to revision was 2.3 years (range, 0.5–5 years) in the 14 revision knee patients and was 1.9 years (range, 0.3–5.4 years) in the 22 revision hip patients. The mean interval of the 2-stage reconstruction was 6 weeks, following the suggestion of Insall and Scott.<sup>4</sup> Patients infected with MRSA required an extra 3 to 4 weeks of antibiotics before re-implantation of prostheses with vancomycin-loaded cement.

The Harris hip scores of revision hip patients improved from a mean of 65 (range, 55–75) to 85 (range, 75–90), with no radiological signs suggestive of loosening at the latest follow-up. Incomplete bone-cement interface lines were not indicative of loosening but did necessitate further follow-up. Knee Society knee scores of the revision knee patients improved from a mean value of 68 (range, 55–75) to 80 (range, 70–85). There were no radiological signs suggestive of loosening at the latest follow-up, according to the guidelines of Knee Society.<sup>2</sup>

## DISCUSSION

Diagnosis of infected joint replacements is by no means straightforward. Besides clinical examination, the diagnostic armamentarium includes blood examination including erythrocyte sedimentation, C-reactive protein, serial radiographs, joint aspirations, differential nuclear and white cell scans, gram stains, and intra-operative frozen section,<sup>5</sup> and newer techniques such as the polymerase chain reaction. Intra-operative culture is widely regarded as a gold standard in the definitive diagnosis of infection.<sup>6</sup> Patients have often received antibiotics prior to revision surgery, making the use of intra-operative frozen section and the judgement of the surgeon crucial to the decision to proceed to a staged reconstruction. On grounds of a highly suspicious intra-operative frozen section alone, 2 patients in this study underwent 2-stage reconstructions (removal of prostheses and use of Prostalac [prosthesis with antibiotic-loaded acrylic cement] followed by re-implantation).

The difficulties in diagnosing these periprosthetic infections, especially in cases of delayed septic loosening of implants (as opposed to acute infection which is easy to diagnose), has been reported by Gristina.<sup>7</sup> The microbe competes with the body's fibroblast in a race 'to the surface' and, upon winning,

many types of pathogenic bacteria form a glycocalyx containing colonies of frequently sessile bacteria. The formation of such 'biofilms' makes it difficult to eradicate these periprosthetic infections. The bacteria inside the biofilm are largely hidden from the body's defence cells, such as polymorphs and macrophages. These sessile bacteria have prolonged multiplication times, which in combination with gene suppression may create a state of near dormancy. It has been estimated that these sessile and near-dormant bacteria are 1000 times more resistant to antibiotics than their planktonic counterparts.<sup>8</sup> It is not until their numbers are so abundant that they spill out of the glycocalyx and are finally detected by the body's defence system that the patient presents with symptoms such as pain.

Both gram-negative bacilli (*Pseudomonas*<sup>9</sup> and *E coli*) and gram-positive bacteria (especially *S aureus* and *S epidermidis*) can form a glycocalyx. *S aureus*,<sup>10</sup> being more virulent than *S epidermidis*,<sup>11</sup> is more frequently implicated in acute infections complicating total joint arthroplasty within 4 weeks of surgery. *S epidermidis* is by far the most commonly implicated microbe in delayed septic loosening of total joint prostheses.

Unlike the conventional 2-stage reconstruction for infected total joint replacements, a current trend is to attempt to retain the prosthesis using intravenous antibiotic therapy plus joint debridement and insert exchange if the infection is diagnosed within 4 weeks of the index arthroplasty.<sup>1</sup> This method, however, is less successful if the culprit organism is *S aureus* instead of *S epidermidis*.<sup>12</sup> In the setting of delayed septic loosening of total joint replacements, although *S epidermidis* has been reported to be the most commonly implicated, infections with gram-negative bacilli have been associated with lower success rates.<sup>13</sup> Two-stage reconstruction is the standard practice in our unit for treating patients with infected total joint arthroplasty. One-stage reconstruction is more popular in Europe, but most hospitals nowadays limit its use to a very select group of patients with good health and low-virulence organisms that do not form glycocalyx.<sup>13</sup>

In this study, *S aureus* was a more common culprit organism than *S epidermidis*, even in late septic loosening of prosthetic implants. Both *S aureus* and *S epidermidis* are prone to developing multiple-drug resistance via their beta-lactamase action or beta-lactam binding proteins. This tendency is mainly due to the rapid horizontal transfer of multiple-drug-resistant plasmids.<sup>14</sup> Recent studies on the nature of staphylococci indicate that the *mecA* gene (located on the staphylococcal cassette chromosome) in *S aureus* is the cause for its methicillin resistance.<sup>15</sup>

It is important to prevent the emergence of multiple-antibiotic resistance by forming close liaisons with different departments and abiding by strict antibiotic administration protocols. Old schemes, such as reserving newer antibiotics for special use or rotating between different regimens, are no longer effective. Different antibiotics have vastly different propensities to the development of resistance, even within the same class. Thus, extra caution should be exercised in the use of antibiotics that are susceptible to resistance (such as tetracycline). Undue caution is not needed if the antibiotics are not (or are uncommonly) associated with resistance such as minocycline. The indiscriminate use of some types of cephalosporin has been implicated in the emergence of the even more fastidious vancomycin-resistant *S aureus*, first reported in Japan and subsequently in other countries.<sup>16</sup> This may represent yet another challenge in the future.

In the event of an outbreak of MRSA, standard outbreak measures<sup>17</sup> should be followed, including isolation, proper hand washing, and the identification and treatment of the source of the infection. Possible sources of an outbreak include patients, medical or nursing staff, and hospital nurseries. Periodic surveillance is imperative, even after the outbreak has been controlled, as nasal carriage is not uncommon even among hospital personnel.

There is a worrying trend toward over-representation of multiple-drug-resistant isolates. A local survey found that 50% of *S epidermidis* isolates were multiple-drug resistant, which coincides with the fact that 50% of the isolates in the current study were

multiple-drug resistant. In the present study, *S epidermidis* and *S aureus* were the predominant causative pathogens, involving 80% of the infected patients from 1997 to 2003 (Table). This resulted in an extensive review of drug protocols, especially antibiotics, throughout the hospital and the strengthening of controls: more stringent periodic screening of the carrier status of medical and nursing staff, treatment of carriers, closer liaison with the microbiology department, and more stringent periodic surveillance of the patterns of antibiotic resistance in every department. Nationwide periodic surveillance of the patterns of drug resistance in major hospitals and comparative studies on both community-acquired and nosocomial strains are important,<sup>18</sup> and the exchange of epidemiological data between countries should be encouraged.

Acute infections treated with antibiotics, debridement, and polyethylene insert exchange are seldom successful if the culprit is *S aureus*.<sup>12</sup> Vancomycin-loaded cement is recommended in joints infected with MRSA; routine administration of vancomycin-loaded cement is not recommended in other cases. MRSA-infected joints often required more than the usual 6 weeks of antibiotic treatment in order to quiet down the clinical and infective parameters such as C-reactive proteins.

Continuous research and development of new drugs to treat fastidious microbes is of paramount importance. A recent investigation into the use of the peptidases to help break down the biofilm and expose the bacteria to antibiotics is probably heading in the right direction.<sup>19</sup>

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