Surgical site infection with methicillin-resistant *Staphylococcus aureus* after primary total hip replacement

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We have analysed the management and clinical outcome of a series of consecutive patients who had a total hip replacement and developed post-operative surgical site infection (SSI) with methicillin-resistant *Staphylococcus aureus*. The incidence of this infection was 1% over a period of five years. We studied SSI in 15 patients (16 infections) with a mean age of 72.7 years (53 to 81). In all, 12 of the infections occurred early and half of the infections involved the prosthesis, resulting in an increase of 11-fold in the cumulative hospital stay.

Methicillin-resistant *Staph. aureus* was successfully eradicated in all the patients after a mean follow-up of 53.6 months (25 to 88). Superficial incisional infections resolved after antibiotic therapy alone while deep infections required multiple operative debridements. Attempted retention of the implant in early organ space infections was successful in only one of five patients. Only three patients with implant-level infections obtained a pain-free, functional prosthesis while a further three required excision arthroplasty. We have formulated a protocol of treatment which may serve as a guide in the management of these infections.

The management of infection after total joint replacement has been compounded by the emergence of organisms with resistance to some antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961 with resistance to methicillin conferred by an extra penicillin-binding protein (PBP2a), which results in a low affinity for beta-lactam antibiotics such as the penicillins and cephalosporins.[1-3] Further virulence is perpetuated in strains capable of producing a biofilm. This slimy matrix, more properly referred to as a glycocalyx, provides a protective barrier from the effects of antibiotics and defences of the host.[4] Some organisms can also remain in a dormant or stationary phase in this matrix, producing resistance against antimicrobials such as beta-lactams which are only effective against rapidly dividing bacteria.[4]

There is an increasing trend in the proportion of MRSA isolates in Europe, with Ireland and the United Kingdom having among the highest at over 40%.[3] A recent multicentre study of 102 hospitals in England showed a rate of surgical site infection (SSI) of 2.2% after total hip replacement (THR) with MRSA being identified as the infecting organism in 24.3%.[5] In a multicentre study in the United States Lee et al[6] found either deep incisional or organ space infection in 1.1% of patients aged over 64 years of age after elective and emergency orthopaedic surgery. Methicillin-resistant *Staph. aureus* was the cause of the infection in 31%.

While measures to prevent the spread of MRSA into elective orthopaedic practice have been described, there are few data available to guide the management of MRSA infection when it occurs after joint replacement.[6-14] No universally-accepted protocol for treatment has yet been proposed. The aims of treatment are to eradicate infection and to restore the use of a pain-free functional prosthesis. Current options include antibiotic therapy, debridement with retention of the prosthesis, and debridement with removal of components followed by direct or delayed exchange arthroplasty.[1,8,15] Arthrodesis, a Girdlestone excision arthroplasty and disarticulation are often considered as salvage procedures.[15] Long-term suppression with antibiotics is a further option when a patient declines or is unfit for surgical intervention.[15,16] The choice of treatment depends on many factors including the acuteness of the infection, the virulence of the organism, the stability of the components and the suitability of the patient for surgery.[1,8,14]

We have analysed prospectively the outcome of MRSA infection after primary THR in a regional Irish orthopaedic centre and assessed

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the effectiveness of current guidelines of best-practice in the clinical setting. We have formulated a treatment algorithm which can be used as a framework for the management of these complex cases.

Patients and Methods

The study sample was taken from a series which we have described previously.[9] Between January 1999 and December 2003, patients with MRSA infection or colonisation in the orthopaedic department of the Merlin Park University Hospital were prospectively identified and entered onto a database. From this group, consecutive cases of MRSA infection after primary THR were selected for analysis. A detailed record was maintained including the clinical management, laboratory investigations, antimicrobial therapy and subsequent operations. The medical notes were examined to identify the place and nature of the patient's residence, medical co-morbidities, subsequent related hospital admissions and the details of the primary THR.

The system used to define the extent of infection has been previously outlined by the Centers for Disease Control guidelines.[17] The three levels described are superficial incisional (skin and subcutaneous tissue), deep incisional (deep soft tissue, muscle and fascia) and organ space (implant) infections. Infections were also classified into early, at less than three months, delayed, presenting at between three months and two years, or late, after two years, based on the presentation of symptoms from the date of the initial joint replacement.[14]

Consultant surgeons (not authors) were involved in all cases either as the principal surgeon or the first assistant. Various implants were used including cemented, uncemented and hybrid systems. All the operating theatres were equipped with laminar air-flow systems. Perioperative antimicrobial prophylaxis was provided as standard in all primary THRs using a second-generation cephalosporin. We gave 1.5 g of cefuroxime intravenously at induction with a further two doses at eight and 16 hours post-operatively.

Suspected cases of infection were investigated initially by measurement of the level of C-reactive protein (CRP; mg/l) and the erythrocyte sedimentation rate (ESR; mm/hr). Confirmation of an infecting organism was by culture of swabs of the wound, intra-operative specimens of periprosthetic tissue and joint fluid if additional surgery was performed, and by blood culture if the patient became pyrexial, which was defined as a core temperature greater than 38°C. Samples were assessed by direct microscopy as well as by aerobic and anaerobic culture. A multidisciplinary approach was applied to all infected patients involving infection control and microbiological services. Patients who were treated with linezolid had weekly haematological studies to monitor for the development of bone-marrow suppression as evidenced by anaemia, leucopenia or thrombocytopenia.

We defined the total stay in hospital as the cumulative duration of all admissions required to manage the infection. For patients with SSI presenting following operation before discharge, the hospital stay was calculated from the date of the initial THR. In the remainder, typically in delayed and late presentations, the total stay excluded the period of the admission for the primary procedure.

A successful outcome was defined by clinical and microbiological evidence of the eradication of infection with MRSA and a stable, pain-free functioning prosthesis.

Results

Elective primary THR was performed in 1790 hips over this period, of whom 18 (1%) developed an infection with MRSA in the wound. Complete data were available for 15 of these patients, six men and nine women with a mean age of 72.7 years (53 to 81) at the time of the operation (Table I). One (case 6) was diagnosed initially with a superficial SSI, but seven months later he presented with a deep infection. This case has been recorded as both a superficial and deep SSI for the purposes of our study giving an overall total of 16 infections for consideration.

Presentation. There were six superficial, two deep and eight infections at the level of the implant (Table I). Classified temporarily, the infections can be considered as 12 early, two delayed and two late infections. Considering the time of onset and the depth of the infection, Figure 1 shows that all superficial SSIs presented early at a mean of 7.8 days post-operatively (5 to 11) whereas deep infection was seen both early at 10 days and delayed at 7.5 months. Infections involving the implant had a more varied timing for presentation, with five early infections occurring at a mean of 9.4 days (4 to 15), one delayed at ten months and two late infections occurring at 6.9 years (3.8 to 10), respectively.

Management and outcome

Superficial surgical site infection. There were six superficial SSIs, all of which were treated with intravenous antibiotics (Table II). Parenteral vancomycin was administered to five patients for durations ranging between five and 18 days. Teicoplanin was given intravenously in one (case 4) for 15 days and subsequently changed to oral linezolid for a further four weeks as an outpatient.

In five patients, after a mean follow-up of 52.8 months (35 to 67), there was no evidence of recurrent infection with MRSA. One (case 6) initially presented with an infected haematoma eight days after operation and was treated with parenteral vancomycin for 18 days until the clinical signs had resolved and biochemical markers were normal. He subsequently returned after 7.5 months with a deep infection, which is discussed below.

Deep surgical site infection. There were two deep SSIs (cases 6 and 7) which required two and three debridements respectively) without removal of the prosthesis, in addition to antimicrobial therapy to eradicate the infection. One patient (case 6) received intravenous antibiotics for six weeks. The other (case 7) was treated for 11 weeks in addi-

Table I. Clinical details, medical co-morbidities and classification of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) in the 15 patients

Case	Gender	Age at primary THR* (yrs)	Residence	Medical co-morbidities†	Implanted system	Time of post-operative presentation	SSI‡ classification	Temporal classification	Acquired§
1	F	72	Home	RA, UTIs	Cemented	11 days	Superficial	Early	HA
2	F	67	Home	HTN	Cemented	8 days	Superficial	Early	HA
3	M	73	Home		Cemented	6 days	Superficial	Early	HA
4	M	79	Home	HTN, DVT	Cemented	9 days	Superficial	Early	HA
5	F	71	Home	CA, JRA, HTN, IHD, asthma	Hybrid	5 days	Superficial	Early	HA
6	M	69	Home		Cemented	8 days	Superficial	Early	HA
						7.5 mths	Deep	Delayed	HA
7	M	70	Home		Cemented	10 days	Deep	Early	POA
8	F	79	Home	AF, HTN	Cemented	9 days	Implant	Early	HA
9	F	74	Home	Anaemia	Cemented	4 days	Implant	Early	HA
10	F	76	Home		Cemented	10 days	Implant	Early	HA
11	F	81	Home	RA, asthma, UTIs	Cemented	3.75 yrs	Implant	Late	POA
12	F	81	Home	PMR, HTN	Hybrid	9 days	Implant	Early	HA
13	F	53	Home	RA	Cemented	10 yrs	Implant	Late	POA
14	M	79	Home	PVD, CA	Cemented	10 mths	Implant	Delayed	POA
15	M	67	Nursing home	HTN, AF	Cemented	15 days	Implant	Early	HA

* THR, total hip replacement

† RA, rheumatoid arthritis; UTIs, recurrent urinary tract infections; HTN, hypertension; DVT, deep-vein thrombosis; CA, malignant disease; JRA, juvenile rheumatoid arthritis; IHD, ischaemic heart disease; AF, atrial fibrillation; PMR, polymyalgia rheumatica; PVD, peripheral vascular disease

‡ SSI, surgical site infection

§ HA, hospital acquired; POA, present on admission

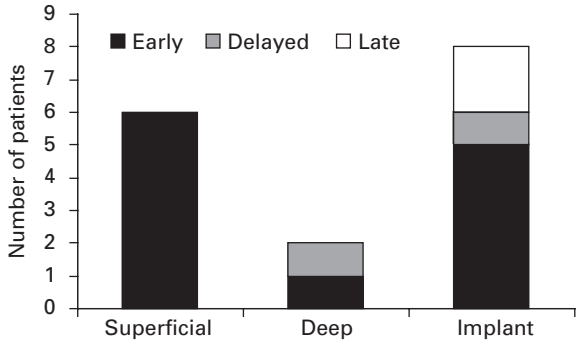

Fig. 1

Bar chart showing classification of methicillin-resistant *Staphylococcus aureus* infection following total hip replacement. Early, less than two months; delayed, three months to two years; late greater than two years.

tion to the placement of vancomycin beads between the second and third debridements. These implant-retaining measures were successful and, at a mean follow-up of 63 months (case 6, 86 months; case 7, 40, months), there has been no evidence of recurrence in either patient. Inflammatory markers had normalised in both hips within three weeks.

Organ-space (implant) surgical site infection. There were eight cases of organ space (implant) infections, five of which were early, one delayed and two late. All the patients received parenteral vancomycin for a mean of 36.8 days (12 to 95). Vancomycin was stopped and oral linezolid was subsequently prescribed in six patients for a mean of 47.2 days (28 to 73). This allowed earlier hospital discharge with outpatient management although additional reasons for changing to oral medication included loss of suitable sites for intravenous access and the occurrence of side-effects of the use of vancomycin. There were no cases of bone-marrow suppression after the administration of linezolid. Adjuvant therapy with rifampicin was given to three patients for a maximum of one week and oral fusidic acid was used in two patients for up to 6.5 weeks. The mean total duration of antibiotic treatment was 72.1 days (45 to 95).

The mean number of operative debridements with irrigation was 3.2 (2 to 5) in all five early presentations of implant infection, but only one patient who also received intravenous antibiotics for a total of 54 days successfully retained the primary implant with no recurrence after follow-up to 64 months. Delayed exchange arthroplasty was attempted in four patients, two with early and two with late infections, with a vancomycin-loaded spacer inserted at removal of the primary THR. In both early infections, successful re-implantation was completed. Iatrogenic femoral shaft fracture complicated one patient (case 12) with subsequent nonunion, resulting in an interval of 24 months before re-implantation. The other (case 18) was uncomplicated with a period of six months between stages; re-implantation in this case was guided by normalising of inflammatory markers. Re-implantation has not been performed in the two patients with late infections of whom one (case 13) who was wheelchair-bound secondary to end-

Table II. Details of the management of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) in the 15 patients

Case	Surgical site infection	Total antibiotic duration (days)	Cumulative stay (days)	Surgical procedures	Follow-up (mths)
1	Superficial	7	22	0	67
2	Superficial	12	29	0	57
3	Superficial	7	15	0	61
4	Superficial	43	32	0	44
5	Superficial	5	17	0	35
6*	Superficial	18	26	0	
	Deep	43	79	2	86
7	Deep	77	49	3	40
8	Implant	54	56	5	64
9	Implant	95	123	5	88
10	Implant	87	175	6	31
11	Implant	45	164	3	38
12	Implant	84	135	4	54
13	Implant	85	52	2	25
14	Implant	64	38	1	9†
15	Implant	63	125	5	61

* developed deep surgical site infection (SSI) seven months after apparent resolution of a superficial SSI
† died after follow-up of nine months from end-stage lung carcinoma

stage rheumatoid arthritis chose not to undergo further surgery. The second patient is awaiting re-implantation. This case was complicated by a femoral shaft fracture that occurred before planned re-implantation; the fracture was subsequently managed conservatively with traction. While union has occurred radiologically and clinically, and infection has apparently resolved both biochemically and clinically, surgery has been deferred until the patient has been medically optimised. An excision arthroplasty (Girdlestone procedure) was the definitive management in the remaining two patients (cases 9 and 12) with early implant infections. They were elderly (74 and 81 years respectively) and chose not to undergo attempted revision surgery given the risk of re-infection with associated additional morbidity.

There was one death (case 14), which was not directly attributable to the MRSA infection. This patient had a delayed presentation and was treated with antibiotic suppression therapy since a subsequent diagnosis of advanced lung carcinoma precluded further surgical intervention. There has been no evidence of recurrent infection with MRSA after a mean follow-up of 51.6 months (25 to 88) in the remainder of patients.

The mean cumulative in-patient stays were 23.5 days (15 to 32) and 64 days (49 to 79) for superficial and deep infections, respectively. Implant infections, accounting for half of all infections, resulted in an 11-fold increase to a mean of 108.5 days (38 to 175).

Discussion

Infection due to MRSA in patients with a THR is a difficult problem to treat effectively. In the absence of a universally-accepted protocol for treatment, patients are generally managed on a case-by-case basis taking account of individual factors. The dilemma of infection with MRSA has been heightened by the emergence of vancomycin-resistant strains as well as increasing reports of community-acquired MRSA infecting normal individuals.[1,16,18,19]

The incidence of infection with MRSA after THR in our unit was 1%. A recent multicentre study in England cited a rate of 0.54%.[5] A significant inter-hospital variation was observed and only infections occurring in the immediate post-operative period before discharge were considered. Had we restricted our series on this basis, our rate of infection for MRSA would have been comparable at 0.67%.

Encouragingly, the overall rate of elimination of infection in our study was relatively high although our management needs to be evaluated according to the level of infection (Fig. 2). Superficial incisional SSI, treated with antibiotics alone, achieved resolution in 83% of patients. The one patient considered to be a failure required antimicrobial therapy for 18 days to resolve the initial infection, but later developed a deep abscess. We believe that superficial infection with MRSA requires intravenous glycopeptides for durations of less than 14 days. If clinical signs of infection are still present at this time, the presence of a deep incisional infection should be considered and investigated further.

Deep incisional infections required multiple aggressive debridement and irrigation to achieve resolution. In-patient glycopeptides were administered for a minimum of five weeks and one patient received additional oral linezolid for six weeks as an outpatient. The inflammatory markers had returned to normal within three weeks in both patients. We consider six weeks anti-MRSA therapy to be adequate for deep incisional infections, however further study may determine a shorter duration to be sufficient. No adjuvant antimicrobials were used for any superficial or deep incisional infections although we could not advise concerning agents such as rifampicin or fusidic acid since further evaluation of antibiotic regimes in larger studies is required.

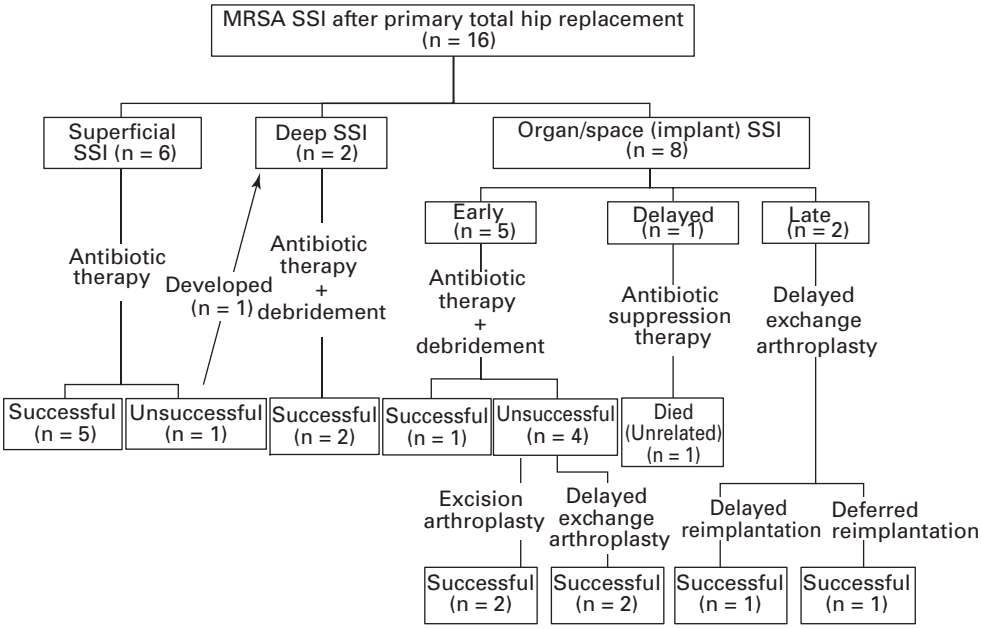

Fig. 2

Flowchart demonstrating the success of methicillin-resistant *Staphylococcus aureus* (MRSA) eradication based on level of surgical site infection (SSI).

Algorithms have been proposed to guide treatment of infection of implants with MRSA.[8,14] Retention of the infected implant has been advocated for early or late infections with a short duration of symptoms, stable components, no significant immunosuppression, and overlying soft tissue and skin of good quality.[8,14] There is no agreement in the literature on the duration of symptoms for which retention should be considered. Davis[8] suggested up to two weeks for early infection and up to 72 hours for acute haematogenous, late, infection whereas Zimmerli et al[14] recommended a period of three weeks for both early and late infections. We attempted debridement and retention of the components in all early implant infections within ten days of the onset of symptoms. This was successful in only one patient who required five surgical debridements and received antibiotic therapy for a total of 7.7 weeks. Given our low rate of success in this limited series, we would caution against salvage procedures in these infections. The inappropriate selection of patients for attempted retention may result in the failure of delayed exchange arthroplasty should the debridements be unsuccessful.[8]

Delayed exchange arthroplasty was completed successfully in two of four patients. Vancomycin-impregnated cement spacers were inserted in the hips between stages to deliver local antibiotic therapy, maintain the length of the limb and to prevent contractures. Opinion is divided on the use of spacers when dealing with MRSA.[8,14] We advocate two-stage reconstruction with an interval of at least six weeks since methicillin-resistant organisms are associated with failure in direct-exchange arthroplasty.[8,14,20,21] Longer intervals may be required with guidance afforded by normalisation of inflammatory markers. In no case in our study was MRSA grown from the tissue specimens taken at re-implantation, but continuation of antibiotic treatment for a further six weeks to three months has been recommended should this happen.[8,14]

There is a general consensus as to the use of the glycopeptides, vancomycin and teicoplanin, as a first-line treatment of infection with MRSA. The addition of rifampicin and fusidic acid has been found to aid eradication, and oral linezolid or weekly parenteral teicoplanin can be considered as an outpatient.[1,8,16,22-24] With the increasing use of glycopeptides strains of MRSA may emerge which are resistant to vancomycin.[1,16] Vancomycin has also been recommended for prophylaxis in joint replacement surgery when conducted in hospitals which have a considerable prevalence of MRSA, although agreement has not yet been reached on what this level is.[24,25]

Excluding the unrelated death in our series, MRSA was eradicated from all patients at a mean follow-up of 53.6 months (25 to 88). A pain-free, functional joint replacement was achieved with all superficial and deep infections, but only three of seven patients with infection involving their implants have a functional THR, including one who retained the original components. Kilgus et al[22] found that six of their 11 patients with THRs infected with MRSA required permanent excision arthroplasty. Based on our

Table III. Proposed management protocol for the management of infection with methicillin-resistant *staphylococcus aureus* (MRSA) in total hip replacement

			Implant SSI			
			Early (< 3 mths)			
Classification	**Superficial SSI***	**Deep SSI**	**< 10 days**	**> 10 days**	**Delayed (3 mths to 2 yrs)**	**Late (> 2 yrs)**
Antimicrobial therapy	Vancomycin IV for 14 days	Vancomycin IV for 6 wks	Vancomycin IV for 6 wks	Vancomycin IV for 6 wks	Vancomycin IV for 6 wks	Vancomycin IV for 6 wks
Surgical procedures	None	Debridement and irrigation	Consider retention: debridement and irrigation Recommend: Delayed exchange arthroplasty	Delayed exchange arthroplasty	Delayed exchange arthroplasty	Delayed exchange arthroplasty
Additional information	Consider deep SSI if clinical signs not resolved after 14 days	Ensure no clinical or microbiological evidence or organ space SSI.	Retention: requires stable implants, no immunosuppression, and overlying soft tissue/skin of good quality likely to require multiple debridements; low success for MRSA eradication			
		May require multiple debridements. Consider adjuvant therapy with rifampicin and/or fusidic acid	Delayed exchange arthroplasty: insert antibiotic-loaded spacer between stages; minimum of six weeks between stages, longer may be required depending on normalisation of inflammatory markers; continue antibiotic therapy for six weeks if MRSA growth from intra-operative cultures at re-implantation; and consider the use of adjuvant antimicrobial therapy such as oral fusidic acid and rifampicin based on local policy and antimicrobial sensitivities			

* SSI, surgical site infection

experience, we suggest a programme of management for treating such infections as outlined in Table III.

Risk factors for the carriage of or infection with MRSA have been described in the literature.[8-11,23,26] It has been established that pre-admission screening, ring-fencing elective orthopaedic beds and prophylaxis with glycopeptides in hospitals experiencing high rates of these infections can reduce this hazard.[7,9,11-13,23,24] The problem of potential MRSA carriage by staff has recently been discussed.[27,28]

Prolonged hospital stay, with the associated requirements of isolation, microbiological costs, and diagnostic tests has been cited as the main factor for the increased cost of managing infection with MRSA.[19,23] With the extended admissions required the costs of treating MRSA infection outweigh those of implementing programmes for screening and prevention.[11] Guidelines for the control and prevention of MRSA have been published by the Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) and specifically recommend that patients undergoing surgery with orthopaedic implants should be screened for MRSA.[29]

Methicillin-resistant *Staphylococcus aureus* has become a prominent cause of infection in hip replacement, typically presenting early, reflecting its high virulence. Treatment is often prolonged, with a high rate of infection of the implant. Given the increasing number of THRs required for an ageing population, infection with MRSA has implications for the future success of joint replacement surgery, the quality of life and of mortality. Aggressive surveillance and compliance with appropriate measures to control infection are necessary to avoid these risks.

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Supplementary Material

A further opinion by Professor S Hughes is available with the electronic version of this article on our website at www.jbjs.org.uk

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