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Infection and sepsis after operations for total hip or knee-joint replacement: influence of ultraclean air, prophylactic antibiotics and other factors

By O. M. LIDWELL*
Formerly of the Cross Infection Reference Laboratory, Colindale, London

E. J. L. LOWBURY
Formerly of the Medical Research Council Burns Unit, Accident Hospital, Birmingham.

W. WHYTE
Building Services Research Unit, University of Glasgow

R. BLOWERS
Formerly of the Medical Research Council Clinical Research Centre and Northwick Park Hospital, Harrow

S. J. STANLEY and D. LOWE
Medical Research Council Biostatistics Unit, Cambridge

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SUMMARY

Operating in ultraclean air and the prophylactic use of antibiotics have been found to reduce the incidence of joint sepsis confirmed at re-operation, after total hip or knee-joint replacement. The reduction was about 2-fold when operations were done in ultraclean air, 4·5-fold when body-exhaust suits also were worn, and about 3- to 4-fold when antibiotics had been given prophylactically. The effects of ultraclean air and antibiotics were additive. Wound sepsis recognized during post-operative hospital stay was, however, reduced by these measures only when it had been classed as major wound sepsis. This was reported after 2·3% of operations done without antibiotic cover in conventionally ventilated operating rooms.

Joint sepsis was much more frequent after wound infection and especially after major wound sepsis, although most cases of joint sepsis were not preceded by recognized wound sepsis. This was particularly noticeable after major wound sepsis associated with *Staphylococcus aureus*; after 37 such infections the same species was subsequently found in the septic joint of 11 patients. The sources of wound colonization with *Staph. aureus*, when this was not followed by joint sepsis, appeared to differ widely from those where joint sepsis occurred later. Operating-

* Requests for reprints to O. M. Lidwell, MRC Common Cold Unit, Harvard Hospital, Coombe Road, Salisbury, Wiltshire SP2 8BW.

room sources could be found for most of the latter and the risk of infection appeared to be similar with respect to any carrier in the operating room whether a member of the operating team or the patient. For wound colonization that was not followed by joint sepsis, operating-room sources could only be inferred for fewer than half and of these more than one half appeared to be related to strains carried by the patient at the time of operation.

During the follow-up period, which averaged about $2\frac{1}{4}$ years with a maximum of four years, there were, in addition to the 86 instances of deep joint sepsis confirmed at re-operation, 85 instances in which sepsis in the joint was suspected during this period but was not confirmed, because re-operation on the joint was not done. The incidence of suspected joint sepsis was, like that of confirmed joint sepsis, less after operations done in ultraclean air: 1/2·5, or with prophylactic antibiotics, 1/2·3

Although re-operation was more frequent on the knee-joint than on the hip, and pain after the initial operation was more frequent after knee operations, there was no evidence that this was the result of any increased risk of infection.

There was some indication of an increased risk of joint sepsis and of major wound sepsis, after operations on patients with rheumatoid arthritis compared with other diagnoses. The increase could have been as much as twofold but, because of the small numbers involved, the statistical limitations of the study render these differences only marginally significant.

When wound washout samples had been obtained from the surgical wound after the insertion of the prosthesis the risk of subsequent joint sepsis was found to be considerably greater for those patients from whose wounds larger numbers of bateria were isolated than from those of other patients at the same hospital.

INTRODUCTION

The role of infection, and particularly airborne infection, as a cause of breakdown of the joint after the insertion of a prosthesis has been the subject of much discussion during the past two decades. It is now clear that bacterial growth in the joint has been responsible for many of the failures and that presumptively causative organisms can be isolated from almost all joints that show signs of sepsis. The species involved, however, are often those considered to have negligible pathogenic potential, e.g. *Staphylococcus epidermidis* or *Propionibacterium* sp. (Whyte *et al.* 1981; Kamme & Lindberg, 1981). The recently published results of a multi-centre prospective randomized study of more than 8000 joint-replacement operations (Lidwell *et al.* 1982, 1983*a*, *b*) have confirmed earlier published reports that reduction in the number of airborne bacteria in the operating room has led to a reduction in the subsequent incidence of joint sepsis (Lindberg, 1979). They also show a substantial reduction in sepsis after peri-operative prophylactic antibiotics.

In this paper, as in our preceding papers, we have used the terms 'sepsis' and 'septic' to mean localized bacterial infection associated with clinically apparent tissue damage. 'Infection', and in particular 'wound infection', has been used to indicate active bacterial multiplication with or without apparent tissue damage, and 'colonization' for bacterial growth without clinical effect.

Table 1. *Joint sepsis in relation to the combined use of ultraclean air and prophylactic antibiotics*

Operating-room conditions		Without antibiotics: No. of operations	Without antibiotics: Septic No.	Without antibiotics: Septic %	With antibiotics: No. of operations	With antibiotics: Septic No.	With antibiotics: Septic %
Control	Observed	1161	39		2968	24	
	Calculated*		39·5	3·4		25·2	0·85
Ultraclean air: conventional clothing	Observed	516	8		1279	9	
	Calculated		8·8	1·7		5·4	0·42
Body exhaust or plastic isolator†	Observed	544	5		1584	1	
	Calculated		4·1	0·76		3·0	0·19

* The calculated numbers and percentage septic have been obtained by assuming, on the basis of the data presented earlier (Lidwell *et al.* 1982, tables II and IV), that the use of ultraclean air halved the sepsis rate, that the use of body exhaust suits in ultraclean air or the use of a plastic isolator reduced the rate to 1/4·5 of that with conventional, control, ventilation and that prophylactic antibiotics further reduced the rates to a quarter of that without their employment; and by setting the calculated total equal to the observed total.

† Trexler (1973).

The reduction in bacterial contamination of the wound due to a cleaner atmosphere and the increased resistance to infection from the use of antibiotics appear to combine together independently and multiplicatively so that, when both protective measures are used, the rate of sepsis can be reduced to a very low figure – no more than a few per thousand operations. This combinatory effect is illustrated in Table 1.

Although the papers cited describe these findings in relation to deep joint sepsis, confirmed as such at re-operation, there are many other aspects of the data that were not reported in these papers. These include: wound infection and sepsis, not apparently involving the joint, during the post-operative period and the relation of this to subsequent joint sepsis; the possible development of sepsis in joints that did not, during the period of study, lead to re-operation ('suspected joint sepsis'); differences in the outcome of the operation according to whether it was on the hip or the knee; and whether the diagnosis was of rheumatoid or osteoarthritis. These and other points will be discussed in this paper.

METHODS

The population studied

The records were obtained from 19 hospitals in England, Scotland and Sweden during 1975–80 and relate to more than 8000 patients. They cannot be taken as representative of all the operations of this kind done in the respective countries. The hospitals and surgeons were chosen by their willingness to take part in a randomized, controlled trial and by the availability of ultraclean air ventilation.

Table 2. *Numbers of patients in relation to age, sex, diagnosis and joint*

Diagnosis and Joint	No. of patients and sex ratio at age: ≤ 55 M	F	F/M	56–70 M	F	F/M	≥ 71 M	F	F/M	Total No.
Rheumatoid										
Hip	52	160	3·1	71	262	3·7	14	86	6·1	645
Knee	49	191	3·9	80	292	3·7	13	99	7·6	724
Osteoarthritis										
Hip	238	333	1·4	1398	1670	1·2	612	1211	2·0	5462
Knee	10	9	0·9	72	181	2·5	42	186	4·4	500
Other										
Hip	109	131	1·2	74	152	2·0	43	166	3·9	675
Knee	7	11	1·6	6	15	2·5	2	5	2·5	46
All diagnoses										
Hip	399	624	1·6	1543	2084	1·4	669	1463	2·2	6782
Knee	66	211	3·2	158	488	3·1	57	290	5·1	1270
All patients	465	835	1·8	1701	2572	1·5	726	1753	2·4	8052

M = male, F = female.

They may, therefore, represent institutions with higher than average standards. This may have affected not only their performance but also the characteristics of the patients admitted to them. Additional details of the study and of the methods employed have been given in Lidwell *et al.* (1982, 1983*a*, *b*).

Table 2 shows the distribution of patients according to age, sex, joint operated on and diagnosis. The most noticeable feature is the excess of females. This is found especially in those diagnosed as having rheumatoid arthritis for which the female/male ratio exceeded three for all ages and both joints.

The increase in the female/male ratio at higher ages is in part a reflexion of the longer survival of females.

When the differences between the individual hospitals were examined, there was little variation in respect of age; on average, 52 % of the patients were over 65, ranging from 40 % to 60 %. The same was true for sex, with an average of 36 % male and a range from 27 % to 47 %.

There were, however, considerable differences in the proportion of rheumatoid patients. The average was 17 % but in seven hospitals the proportion exceeded 20 %, with a maximum of 34 %; in the remainder it was less than 13 %, with the lowest under 1 %. There was similar variability with regard to the joint operated on: while the average proportion of operations on the knee was 16 %, at six hospitals none was recorded. The highest proportion was 41 %. The joint affected and the nature of the disease were highly correlated: rheumatoid arthritis was diagnosed in 47 % of the knees but in only 9·5 % of the hips. However, as will be shown later, neither the joint affected nor the disease diagnosed was sufficiently correlated with the development of joint sepsis for these inter-hospital variations to contribute significantly to the differences between the observed risk of sepsis at the different hospitals.

The outcome of the operation: sepsis and pain

Patient data were recorded at each hospital, usually by a part-time nurse engaged for that purpose, on a series of record cards. The first of these included basic details of the patient and the operation. The second assembled information during the post-operative in-patient stay; if this was prolonged, several of these cards were needed. The third card recorded similar information after discharge; again several such cards might be needed. A fourth card was used if the patient was readmitted for another operation on the same joint and a fifth at those hospitals where records of carriage of *Staphylococcus aureus* by the patient and operating-room staff at the time of the initial operation had been obtained. On the basis of the recorded information the outcome of the operation was assessed in the following ways:

(*a*) *Wound sepsis, in-patient.* This was initially divided into four grades on the basis of the surgeons' recorded clinical assessment:

(1) No evidence of wound sepsis.
(2) Possible wound sepsis.
(3) Minor wound sepsis.
(4) Major wound sepsis.

In a later section of this paper these assessments are discussed in relation to the recorded signs and symptoms.

(*b*) *Wound sepsis, out-patient.* This was assessed in the same way as in-patient wound infection.

(*c*) *Joint sepsis, when joint re-operated*: The method of assessment of this has already been described (Lidwell *et al.* 1982). After scrutiny of the patient records three grades were distinguished:

(1) No evidence of joint sepsis.
(2) Some evidence of possible joint sepsis.
(3) Strong evidence of joint sepsis; 'confirmed' joint sepsis.

(*d*) *Joint sepsis, joint not re-operated.* This was based entirely on the surgeons' assessment. Without re-operation the diagnosis of bacterial sepsis could not be confirmed. It was classified as:

(1) No suspicion of joint sepsis.
(2) Suspected joint sepsis.

(*e*) *Abnormal pain in the joint.* This was recorded as:

(1) Non-weight-bearing, in-patient.
(2) Weight-bearing, in-patient.
(3) Non-weight-bearing, out-patient.
(4) Weight-bearing, out-patient.

(*f*) *Any abnormal signs recorded post-operatively.*

RESULTS

The data which form the basis of the analysis were randomized in relation to the type of ventilation in use in the operating rooms at the time of the operation for the insertion of the prosthesis. Any evaluation of the effects of other treatments or procedural variations, including the perioperative use of antibiotics, is to some extent confounded with variation in the risk of infection at different hospitals and between operations done by different surgeons. The extent to which this limitation prevents or invalidates evaluation varies with the different factors. In relation to what is probably the most important of these, namely the use of perioperative antibiotics, the relevant considerations have already been discussed (Lidwell *et al.* 1982), and reasons have been given for believing that the apparent large reduction in the risk of joint sepsis was for the most part genuinely due to the effects of antibiotics.

Ventilation and antibiotics

The incidence of the sequelae to the operation listed above are given in Table 3 in relation to operating room ventilation and the use of prophylactic antibiotics. During the period of in-patient stay, major wound sepsis was reported after 2·3 % (27/1161) of operations done without antibiotic prophylaxis in conventionally ventilated operating rooms and minor wound sepsis after 5·1 % (59/1161). For operations done in ultraclean air, without antibiotic prophylaxis, the corresponding figures were 0·7 % (7/1060) and 5·2 % (55/1060), and for operations in conventionally ventilated rooms with antibiotic prophylaxis 0·6 % (17/2968) and 3·7 % (111/2968). From these figures, and from the incidence ratios given in Table 4 it appears that operating in ultraclean air and the use of perioperative antibiotics separately and together, reduced the incidence of major wound sepsis and that the incidence of minor wound sepsis was reduced by the use of antibiotics, but not by operating in ultraclean air.

The instances of wound sepsis first reported after discharge of the patient from hospital, shown in Table 3 but not in Table 4, were very few but generally followed a similar pattern.

The substantial reductions in joint sepsis, when this was confirmed at re-operation, have already been reported (Lidwell *et al.* 1982). The data for the 85 patients with suspected joint sepsis are of considerable interest. Few, if any, symptoms other than abnormal pain in the joint were recorded in these cases but the incidence appears to have been reduced by a factor of 2·16 when operating in ultraclean air, and by a factor of 2·33 when prophylactic antibiotics were given; an extent similar to, if somewhat less than, that for confirmed joint sepsis. From this it seems reasonable to infer that most of the joints in which sepsis was suspected were in fact infected.

There were various reasons why these patients did not come to be re-operated, e.g. (*a*) the condition was not so severe as to demand re-operation, either in the judgement of the surgeon or in the willingness of the patient; (*b*) the infection responded to treatment with antibiotics; (*c*) the study ended, or the patient died, before sepsis had developed to the extent that re-operation was required. Follow-up of these 85 patients for a longer period may reveal how often the condition worsened so as to need re-operation and if so whether this was due to bacterial infection.

When the incidence of confirmed joint sepsis and suspected joint sepsis at the individual hospitals were examined there was a strong correlation between the two ($r = 0{\cdot}67$, $P < 0{\cdot}01$). This would be expected if both were derived from bacterial contamination at the time of operation. There was, however, no significant

Table 3. *Outcome of total joint replacement operations. Number* of instances with the specified abnormal sequela*

			Assessment of wound infection						Assessment of joint sepsis				Abnormal pain			
		No. of operations with any	in-patient			out-patient			reoperation			no reop-eration	in-patient		out-patient	
Conditions	Total operations	post-operative abnormality	2	3	4	2	3	4	1	2	3	2	non-weight	weight	non-weight	weight
C1.N*	641·0	261·1	31·9	37·1	19·2	1·0	0·0	4·0	21·4	2·8	23·8	22·5	13·2	8·8	35·0	65·6
C2.N	520·0	187·9	7·1	21·9	7·8	1·0	2·0	2·0	9·6	4·2	15·2	10·5	6·8	4·2	10·0	32·4
C1.AB	1401·9	464·5	52·8	58·6	10·4	4·0	2·4	4·2	44·4	6·8	12·7	12·3	13·9	11·4	65·2	130·1
C2.AB	1566·1	554·5	45·2	52·4	6·6	0·0	2·6	3·8	45·6	6·2	11·3	13·7	59·1	16·6	73·8	137·9
UC1.N	515	181	18	26	4	2	4	0	21	5	8	6	12	4	31	54
UC1.AB	1274	484	56	51	13	5	0	1	63	8	9	10	32	16	84	156
UC2.N	545	164	10	29	3	0	1	0	7	5	5	1	11	8	8	15
UC2.AB	1589	522	36	32	0	3	0	0	32	3	1	9	53	23	62	123
Total	8052	2819	257	308	64	16	12	15	244	41	86	85	201	92	369	714

C1 and C2 = control series, conventional ventilation and clothing; UC1 = ultraclean air with conventional pattern clothing, matched with C1; UC2 = ultraclean air with body-exhaust suits, or a plastic isolator, matched with C2, N = Prophylactic antibiotics not given; AB = antibiotics given perioperatively.

Wound infection: 1 = no evidence of sepsis, 2 = some evidence, possible sepsis, 3 = minor wound sepsis, 4 = major wound sepsis.

Joint sepsis: re-operated, 1 = no evidence of sepsis, 2 = sepsis possible, but doubtful, 3 = confirmed sepsis; not re-operated, 2 = suspected sepsis.

* The observations in the control series, at those hospitals where operations were done in the UC1 and in the UC2 series, have been apportioned in proportion to the numbers of operations done in those hospitals in the respective series so as to provide unbiased comparisons between the control and ultraclean air series. This leads to fractional values for the purposes of the comparisons. The actual total numbers done under the control conditions are obtained by adding C1.N to C2.N and C1.AB to C2.AB.

Table 4. *Wound and joint sepsis in relation to operating conditions*

	Overall incidence (%)	Incidence ratios for conditions compared* C/UC (Conv.)	C/UC (BE, Isol.)	C/UC (All)	N/AB
Wound infection (in-patient)					
Possible infection	3·19	1·00	1·16	1·08	0·93
Minor wound sepsis	3·83	1·09	1·25	1·17	**1·54**
Major wound sepsis	0·79	1·52	**4·91**	**2·09**	**2·97**
Joint: not re-operated					
Suspected sepsis	1·06	*1·90*	*2·48*	**2·16**	**2·33**
Joint: re-operated					
No evidence of sepsis	3·03	*0·68*	1·45	0·93	0·84
Possible sepsis	0·51	0·65	1·33	0·90	1·86
Confirmed sepsis	1·07	*1·88*†	**4·54**	**2·60**	**4·02**
Pain: in-patient					
Non-weight-bearing	2·50	**0·54**	1·05	0·82	*0·71*
Weight bearing	1·14	0·88	0·69	0·76	0·98
Pain: out-patient‡					
Non-weight bearing	4·58	*0·76*	1·23	0·94	*0·77*
Weight bearing	8·87	*0·82*	1·26	1·00	*0·80*

* C = control series, conventional ventilation; UC = operations done in ultraclean air; N = prophylactic antibiotics not given; AB = prophylactic antibiotics given; (Conv.) = conventional pattern operating room clothing worn; (BE, Isol.) = body-exhaust suits worn or patient attached to a plastic isolator. The ratios are derived from the figures given in Table 3, e.g. that for

$$\text{C/UC (Conv.) for major wound sepsis} = \frac{19{\cdot}2+10{\cdot}4}{641{\cdot}0+1401{\cdot}9}\times\frac{515+1274}{4+13} = 1{\cdot}52;$$

combining operations with and without antibiotic prophylaxis. Values given in italics are significantly different at the $P < 0{\cdot}05$ level; bold type $P < 0{\cdot}01$.

† In this table, 1, 3 and 4 of table II (of Lidwell *et al.* (1982) have been combined, which accounts for the ratio 1·88, as against 2·0 for groups 1 and 3 only.

‡ Any time after initial discharge.

correlation between the risk of re-operation without evidence of infection and the risk of confirmed joint sepsis at the individual hospitals ($r = 0{\cdot}39$, $P > 0{\cdot}1$).

Wound infection and sepsis

The assessment of wound sepsis on clinical grounds is potentially liable to considerable variation according to the judgement of the surgeon or other person recording the condition. In an attempt to obtain a more objective assessment the state of the wound was recorded, both during in-patient stay after the operation and on subsequent recall, using a standard format.

The signs recorded are given in Table 5, together with the frequency with which they were associated with the four levels of clinical assessment. Good correspondence between the recorded signs and the clinical assessment could not be achieved over the whole body of data, either by the use of weighted scoring systems or by various forms of regression analysis. The relatively poor correspondence undoubtedly reflects the difficulty of clinical assessment, and variation in this between surgeons and hospitals. Although there were large proportionate differ-

Table 5. *Frequency of recorded signs and clinical assessment of in-patient wound infection*

Sign	Number (percentage) of patients with: No evidence of sepsis	Possible sepsis	Minor sepsis	Major sepsis	Total
Abnormal redness	261 (4)	68 (27)	77 (25)	19 (30)	425
Gaping	249 (4)	58 (23)	78 (26)	23 (36)	408
Sinus	30 (1)	5 (2)	15 (5)	16 (25)	66
Haematoma	286 (4)	36 (14)	45 (15)	17 (27)	384
Discharge without polymorphs*	914 (12)	153 (60)	174 (57)	20 (31)	1261
Discharge with polymorphs	36 (1)	21 (8)	70 (23)	39 (61)	166
Abscess	19 (1)	3 (1)	9 (3)	6 (9)	37
Pyrexia, above 37·8 °C, beyond 8 days	276 (4)	36 (15)	29 (10)	22 (35)	363
ESR > 20 mm/h beyond 8 days	1501 (22)	66 (27)	123 (41)	34 (54)	1724
Pathogenic bacteria isolated†	229 (3)	67 (20)	217 (70)	49 (77)	562
Staph. aureus isolated	75 (1)	29 (11)	117 (38)	37 (58)	258
None of above recorded	4615 (62)	9 (4)	6 (2)	0 (0)	4630
Total	7423	257	308	64	8052

* Polymorphs not recorded at any time.

Patient observations were not recorded for 227 patients (2·8 %): 222 of these were entered as without any evidence of wound sepsis, two as having possible sepsis and three as exhibiting minor wound sepsis.

† Including: *Staph. aureus*, streptococci, Enterobacteriacae (e.g. *E. coli*, *Klebsiella* spp., *Proteus* spp.), *Pseudomonas* spp., *Bacteroides*, spp. *Clostridia* spp. and other anaerobic bacteria.

ences in the relation between the reported incidence of clinical wound sepsis and that of specific signs at different hospitals, the small number of instances at any one hospital meant that none of these reached statistical significance at the 0·05 level. Closer agreement could certainly be obtained by considering the data for individual hospitals separately but the purpose of the procedure was to attempt to define the condition more objectively in a way that would apply to the whole of the study. There was also some recording error, e.g. 36 patients with wound discharge containing polymorphs, from six of whom pathogenic bacteria were isolated, were recorded as without any sign of clinical sepsis. On the other hand, minor sepsis was reported for six patients for whom abnormal signs were not recorded. Only the frequency of '*Staph. aureus* isolated' and of 'Discharge with polymorphs', among the signs listed in Table 5, appeared to be significantly related to the ventilation conditions and the use of prophylactic antibiotics ($P < 0{\cdot}01$) *Staph. aureus* was isolated from the wound more than three times as often in the absence of antibiotic prophylaxis. Wound discharge with polymorphs was about 50 % more frequent after operations done in conventionally ventilated rooms than for those done in ultraclean air and similarly more frequent after those operations done without antibiotic prophylaxis, compared with those where this had been given.

Table 6. *Wound infection and later joint sepsis*

	No. of patients with				
	No evidence of wound infection	Possible wound infection	Minor wound sepsis	Major wound sepsis	
Total no.	7423	257	308	64	8052
Joint not re-operated					
Suspected sepsis	60 (0·8)	7 (2·7)	9 (2·9)	9 (14·1)	85 (1·1)
Joint re-operated					
No evidence of sepsis	207 (2·8)	13 (5·1)	6 (1·9)	8 (12·5)	234 (3·0)
Possible sepsis	32 (0·4)	0 (0·0)	3 (1·0)	6 (9·4)	41 (0·5)
Confirmed sepsis	51 (0·7)	8 (3·1)	8 (2·6)	19 (29·7)	86 (1·1)

In parentheses, percentage of total with that assessment of wound infection.

Wound infection in relation to later joint sepsis

Table 4 shows that major wound sepsis reported during the initial in-patient stay after operation, like confirmed joint sepsis, was influenced by the operation conditions, by ultraclean air and by antibiotic prophylaxis. These wound infections will usually have involved the deeper tissues. Any influence of ventilation on the incidence of minor wound sepsis, generally superficial, was small and not significant. There was, however, some evidence that minor wound sepsis was reduced by prophylactic antibiotics. It is, therefore, of interest to examine the relationship between early wound infection and subsequent joint sepsis. This is shown in Table 6. It is apparent that the risk of joint sepsis was much greater (19/64 = 30 %) after major wound sepsis and was somewhat greater (16/565 = 3 %) after any suspicion of wound sepsis than when there was no evidence of wound sepsis at all (51/7423 = 0·7 %). The difference was similar in the control series to that in the total data. These results are similar to those recently published by Surin and colleagues (1983) for a series of 803 hip-joint replacements during 1970–77. Using wound discharge as the criterion, the risk of subsequent joint sepsis, compared with that when wound healing was uneventful, was doubled if the discharge was sterile and increased sixfold if this was infected.

A similar pattern is also apparent for the cases of suspected joint sepsis, 14 % of the cases of major wound sepsis were followed by suspected joint sepsis, for minor wound sepsis or possible wound infection the corresponding figure was about 3 % while if there had been no indication of wound sepsis it was less than 1 %. These proportions are in addition to those for confirmed joint sepsis so that more than 40 % of the instances of major wound sepsis were followed by either confirmed or suspected joint sepsis; however, two-thirds of the combined number of instances of confirmed or suspected joint sepsis were not preceded by any indication of wound sepsis, and fewer than 20 % by major wound sepsis.

The bacteria isolated from wounds during the post-operative period of hospital stay are shown in Table 7. The extent of bacteriological investigation, when there was no indication of wound infection, varied greatly from hospital to hospital. In some, virtually all wounds were so examined, in others only a small proportion. However, almost all those wounds, where there was evidence of sepsis were examined bacteriologically.

Table 7. *Isolation of bacteria from the wound and later joint sepsis*

	Number (percentage) of patients with:				
	No evidence of wound sepsis	Possible wound sepsis	Minor wound sepsis	Major wound sepsis	Total
Wound examined bacteriologically	2545 (34)	218 (85)	301 (98)	61 (95)	3125 (39)
Staph. aureus isolated from wound	75	29	117	37	258
Staph. aureus in later septic joint	10	1	4	12	27
After *Staph. aureus* in wound	0	1	4	11	16
Similar phage type in wound and joint*	0	1	2	9	12
Intestinal species† isolated from wound	150	31	114	33	328
Intestinal species in later septic joint	7	0	1	3	11
After same intestinal species in wound	1 (+1)‡	0	1	2	4 (+1)
Streptococci§ isolated from wound	34	15	34	5	88
Streptococci in later septic joint	4‖	1	0	0	5
Any 'pathogen' isolated	229	67	217	49	562
Other bacterial species¶ isolated from wound	727	76	139	31	973
Later joint sepsis with these species	20	2	0	3	25
After wound infection with these species**	2	0	0	2	4
Any isolation	842	127	277	57	1303
All joints with confirmed sepsis:					
Wound infection with species later found in joint	3 (+1)	1	5	15	24 (+1)
Different species isolated from wound and joint	2	0	0	2	4
No isolation from wound	44	6	1	1	52††

* Complete phage-typing data available for only 14 out of the 27 instances of joint sepsis with *Staph. aureus*; for only one of these did the wound and joint strains differ.

† Intestinal species include *E. coli*, *Pseudomonas* spp., *Alkaligenes faecalis*, *Proteus* spp.

‡ Mixed intestinal species isolated from wound and from septic joint but *same* species not recorded in both.

§ More than two-thirds of these isolates were faecal streptococci, another 10 % were β-haemolytic streptococci, but there was no isolation of group-A streptococci.

‖ A group-B streptococcus was isolated from one of these septic joints. Faecal streptococci were isolated from the other four joints. In *no* instance was the same species found previously in the wound.

¶ Other species, excluding any normal for the site, included *S. albus* (*epidermidis*), *Propionibacter* spp., coryneform bacteria, gram-positive cocci, anaerobic cocci.

** Without evidence that wound and joint carried the *same* species but these are included in the numbers given in the next but one following row.

†† Bacteria were isolated postoperatively from the wounds of five patients who subsequently suffered confirmed joint sepsis but no bacteria were isolated from the joint. These five complete the total of 86 joints with confirmed sepsis.

Wound infection with *Staph. aureus* was more frequently followed by joint sepsis with the same organism, 11/37 after major sepsis and 16/183 after any indication of wound sepsis, than was the case for other species, 4/69 after major sepsis and 5/478 after any indication of wound sepsis.

In the great majority of instances when joint sepsis had been preceded by any indication of wound sepsis, the species isolated from the joint were the same as those that had been isolated from the wound postoperatively. This was so for 16/17 instances of joint sepsis associated with *Staph. aureus* and for 3/5 instances of joint sepsis associated with intestinal species. For the *Staph. aureus* joint infections phage-typing data were available for 14 and in only one instance did the wound and joint strains differ.

Sources of wound infection with Staphylococcus aureus

In some operations the patient, the surgeon, the anaesthetist and other scrubbed members of the operating room staff had been examined for carriage of *Staph. aureus* at the time of operation (Lidwell *et al.* 1983*a*). This had been done and the strain had been phage-typed, for 115 of the 258 instances in which *Staph. aureus* was subsequently isolated from the wound during in-patient stay (Table 8). For 36 of these 115 wound strains, a strain with a closely similar or identical phage pattern had been isolated from a person in the operating room at the time of operation, and could be considered to be a probable source for the wound infection. For 55, no strain considered similar to the wound strain was found among those persons in the operating room. Eighteen of the remaining 24 were non-typable strains and a non-typable strain with similar characteristics was carried by some person in the operating room at the time of operation; 9 of these 18 involved one surgeon. For the remaining 6, strains had been isolated from persons in the operating room with phage-typing similarities such that they could have been the source of the wound infection. All these 24 operating-room strains have been classed as 'possible' sources. These proportions are very similar to those reported by one of us 20 years ago (Blowers, 1963) when among 55 instances of wound sepsis with *Staph. aureus* only 12 sources among the scrubbed staff in the operating room and 9 from the patient could be identified. The detailed attribution of sources for the wound strains and for those isolated later from septic joints (Lidwell *et al.* 1983*a*) is given in Table 8. Generally the determination of similarity between the wound strain and its probable or possible source was much easier than for the joint strains, possibly due to the often considerable time interval between the isolations to be compared in the latter case.

For 11 of the 14 cases of joint sepsis the strain isolated from the joint was similar to one previously isolated from the wound. In only one case, for which a possible source was not identified for either strain, did the strain isolated from the joint clearly differ from one previously found in the wound.

The distribution of sources for the strains which were isolated from wounds that were not followed by joint sepsis was very different from that for the strains associated with joint sepsis. A possible operating-room source could be predicated for most, 12/14, of the instances of joint sepsis, and the probability of this seemed to be similar for all carriers. In contrast, probable or possible sources for the wound strains not followed by joint sepsis were found for less than half (50/103) and, of

Table 8. *Sources of infection with* Staphylococcus aureus

	No. of instances from:							
	Assistants		Surgeon		Patient		No source found	Total
	Probable	Possible	Probable	Possible	Probable	Possible		
Staph. aureus isolated from wound without later confirmed joint sepsis								
No evidence of wound sepsis	0	2	0	6	6	1	9	24
Possible wound sepsis	0	1	0	½	4	½	9	15
Minor wound sepsis	8	1	1	2	10	4	28	54
Major wound sepsis	0	½	0	0	2	½	7	10
All	8	4½	1	8½	22	6	53	103
Staph. aureus isolated from wound followed by joint sepsis with the same species								
No evidence of wound sepsis	0	0	0	0	0	0	0	0
Possible wound sepsis	1	0	0	0	0	0	0	1
Minor wound sepsis	0	1	0	1	0	0	0	2
Major wound sepsis	2	3	1	0	1	0	2*	9
All	3	4	1	1	1	0	2	12
Staph. aureus not isolated from wound but joint sepsis with this species confirmed subsequently	1	0	0	0	1	0	0	2

An entry of ½ indicates two possible sources. Of the 19 'possible' sources for wound sepsis without subsequent joint sepsis, 16, including all 8½ related to the surgeon, involved a non-typable strain. This was the case for only two of the five 'possible' sources of joint sepsis. For 11 of the 14 cases of joint sepsis, the joint strain was the same as that previously isolated from the infected wound; in only one case, where no 'probable' or 'possible' sources were identified, *, did the joint strain differ from that previously isolated from the infected wound.

these, 28 appeared to have been derived from the patient. This difference in source distribution suggests that the method of infection for most instances of wound infection is not the same as for joint sepsis. In particular the data are consistent with wound infection often arising after the patient had left the operating room, when the patient was the only source identifiable in our data.

In view of this difference, the cases of major wound sepsis, the only grade to show any significant effect of operating-room conditions, have been subdivided according to whether or not they were followed by joint sepsis. Because confirmed joint sepsis and suspected joint sepsis show similar correlations with operating-room conditions these two grades have been combined for this purpose. When this is done the incidence of major wound sepsis followed by joint sepsis, confirmed plus suspected, differs according to the operating circumstances much more than does that of major wound sepsis when joint sepsis did not occur later. When followed by joint sepsis, the incidence of major sepsis for operations done without antibiotic prophylaxis was 7·9 times that for operations done with such prophylaxis; and the incidence for operations done in conventionally ventilated operating rooms was 2·8 times that for operations done in ultraclean air. When, however, major wound sepsis was not followed by joint sepsis the corresponding ratios were 1·5 and 1·7 respectively. The numbers are rather small but confirm the greater influence of perioperative conditions the more severe, or deeper, the infection.

Comparison between the outcome of hip and knee operations

Comparison between the probabilities of the various outcomes of operations on the hip or the knee is shown in Table 9. There was a high degree of correlation between the joint operated on and the incidence of a rheumatoid diagnosis. The ratio of the incidence for the several outcomes as between operations for replacement of the knee and those for replacement of the hip joint are therefore shown as: (*a*) the simple ratio of incidence; (*b*) the ratio corrected by indirect standardization for the distribution of operations between ventilation conditions and the use of antibiotics; and (*c*) after also making allowance in a similar way for the correlation with diagnosis. When this is done the only significant ratios are for pain and re-operation without evidence of infection, which lie between 2·58 and 4·11. These certainly reflect the higher incidence of mechanical failure after operations for replacement of the knee joint, in this series about three times greater than for the hip. The somewhat higher incidence of suspected infection in knees, a ratio of 2·15, may be due to this, rather than to infection, because the clinical diagnosis was largely related to the occurrence of abnormal pain.

Outcome in relation to the type of joint disease

A similar analysis has been done in relation to the aetiology of the condition for which the joint replacement operation was done (Table 10). There were no differences, significant at the 0·05 level, between the incidence of confirmed or suspected joint sepsis after operations on rheumatoid joints compared with the others, predominantly osteoarthritic, when allowance is made for the correlation between the joint operated, knee or hip, and diagnosis; however, the ratio for confirmed sepsis, 1·28, approaches significance at this level. The ratio in respect of major in-patient wound sepsis, 2·11, just reaches significance at the 0·05 level. In

Table 9. *Wound and joint sepsis in relation to joint (hip or knee) operated on*

	Overall incidence (%) (hip or knee together)	Ratio knee/hip*		
		(*a*)	(*b*)	(*c*)
Wound infection (in-patient)				
Possible infection	3·19	1·23	1·06	0·91
Minor wound sepsis	3·83	**1·51**	**1·48**	1·38
Major wound sepsis	0·79	1·78	1·64	1·08
Joint: not re-operated				
Suspected sepsis	1·06	*1·75*	*1·77*	*2·15*
Joint re-operated				
No evidence of sepsis	3·03	**2·91**	**2·45**	**2·58**
Possible sepsis	0·51	**2·48**	**2·46**	2·09
Confirmed sepsis	1·07	1·32	1·41	1·03
Pain: in-patient				
Non-weight bearing	2·50	**2·33**	**2·42**	**2·83**
Weight bearing	1·14	**2·85**	**3·00**	**4·11**
Pain: out-patient†				
Non-weight-bearing	4·58	**2·64**	**2·28**	**2·81**
Weight bearing	8·87	**2·60**	**2·29**	**2·76**

Values in italic are significantly different at the $P < 0{\cdot}05$ level, bold type $P < 0{\cdot}01$.

* (*a*) Simple incidence ratio; (*b*) ratio corrected for operating room ventilation and antibiotic prophylaxis; (*c*) ratio also corrected for joint/diagnosis correlation; weighted for numbers of operations with rheumatoid or other diagnosis.

† Any time after initial discharge.

Table 10. *Wound and joint sepsis in relation to aetiology*

	Overall incidence (%)	Ratio; rheumatoid/other*		
		(*a*)	(*b*)	(*c*)
Wound infection (in-patient)				
Possible infection	3·19	1·21	1·06	0·92
Minor wound sepsis	3·83	*1·41*	*1·38*	1·22
Major wound sepsis	0·79	**2·38**	**2·25**	*2·11*
Joint: not re-operated				
Suspected sepsis	1·06	1·13	1·16	1·09
Joint: re-operated				
No evidence of sepsis	3·03	**1·70**	**1·47**	0·95
Possible sepsis	0·51	1·79	1·81	0·90
Confirmed sepsis	1·07	1·48	1·60	1·28
Pain: in-patient				
Non-weight bearing	2·50	**1·57**	**1·66**	*1·59*
Weight bearing	1·14	1·44	1·49	1·53
Pain out-patient†				
Non-weight bearing	4·58	1·27	1·16	0·80
Weight bearing	8·87	*1·23*	1·11	**0·54**

Values in italic are significantly different at the $P < 0{\cdot}05$ level, bold type $P < 0{\cdot}01$.

* 'Other', osteoarthritis together with a small number, 10%, of miscellaneous conditions.

† Any time after initial discharge.

(*a*) Simple incidence ratio; (*b*) ratio corrected for operating room ventilation and antibiotic prophylaxis; (*c*) ratio also corrected for joint/diagnosis correlation; weighted for numbers of hip and knee operations patients with a rheumatoid diagnosis, there was an excess of pain during the in-patient period, but pain was less frequently reported, especially on weight-bearing, after initial discharge from hospital. The overall impression is that the incidence of infection and sepsis was probably higher in patients with rheumatoid arthritis but that the difference was not large enough to reach more than marginal statistical significance in this study.

The bacterial species associated with joint sepsis and the interval between insertion of the prosthesis and re-operation on the joint were examined for patients with rheumatoid arthritis and compared with those for other diagnoses.

There was a somewhat higher proportion of instances of sepsis due to *Staph. aureus* in the rheumatoid group 9/18 compared with 16/68 for other diagnoses, entirely associated with operations on the knee, and a tendency for re-operation to be performed earlier, 4/19 in the three months after operation compared with 7/68 for non-rheumatoid patients, again associated with operations on the knee, but in view of the small numbers involved the differences are of doubtful significance.

Steroids

A minority of the patients (482/8052, 6·0 %) had received steroids within the 48 h before operation, 74 % of these had a diagnosis of rheumatoid arthritis. While steroids were given to less than 2 % of patients with other forms of arthritis they were administered to 20 % of the rheumatoid patients.

The apparent effects of treatment with steroids were similar to those described above as associated with a diagnosis of rheumatoid arthritis. In view of the high degree of correlation between this diagnosis and the giving of steroids, it is not possible within this small subgroup of data, to distinguish between the effects of the two factors.

DISCUSSION

Previously published results from the study (Lidwell *et al.* 1982, 1983*a*, *b*) have demonstrated the reduction in joint sepsis, confirmed at subsequent re-operation after total hip or knee-joint replacement, when the operation was done in operating rooms ventilated so as to reduce the level of airborne contamination substantially. The additional data presented here show that the frequency of joint sepsis suspected by the surgeon when, for a variety of reasons, a re-operation had not been done by the end of the period of study was also substantially less when the prosthesis had been inserted in an ultraclean air environment. The frequency of suspected joint sepsis, like that of confirmed joint sepsis, was also less when antibiotics and been given prophylactically. The influence of airborne contamination on the incidence of post-operative wound infection and sepsis as distinct from joint sepsis is of considerable interest, because it may suggest a similar effect on other types of operation which may not be as susceptible as hip or knee-joints to sepsis developing slowly or from infection with organisms of low pathogenicity. Any substantial benefit from ultraclean air was demonstrated only for the minority of wounds that suffered from major sepsis (about 2·3 % after operations done in conventionally ventilated operating rooms without antibiotic prophylaxis). The incidence of these wound infections was also reduced by antibiotic prophylaxis.

The effect of perioperative conditions on the incidence of major wound sepsis was therefore parallel to that on the incidence of joint sepsis. These wounds will generally have involved deeper tissues, but fewer than one-third were followed by confirmed joint sepsis. The incidence of major wound sepsis did not appear to be influenced by operating-room conditions to as great an extent when not followed by joint sepsis as it did when this occurred later. There was also some indication, not statistically significant, that minor wound sepsis was reduced to a small extent by ultraclean air ventilation. It was, however, significantly reduced by prophylactic antibiotics.

Several authors have reported a substantially higher incidence of joint sepsis after the insertion of the prosthesis in patients with rheumatoid arthritis than in those with osteoarthritis, e.g. Charnley (1979) reported an incidence of 9/468 as against 17/4176 a ratio of 4·7 with 95% confidence limits of 10·6–2·1, and Fitzgerald & colleagues (1977) reported an incidence of 7/223 against 16/2103 a ratio of 4·2 with 95% confidence limits of 10·2–1·7. However, Lidgren (1973) has reported no evidence of any increase in the risk of sepsis in patients with rheumatoid arthritis, compared with other diagnoses, after orthopaedic operations and Poss *et al.* (1976) recorded an identical incidence of deep joint infections after total hip replacement in patients with rheumatoid arthritis (4/275) and in those with osteoarthritis (6/382); confidence limits for the incidence ratio are 3·2–0·25. Our data, when corrected for differences in antibiotic prophylaxis and the environment in which the operation was done, show only moderate differences associated with the diagnosis. There were proportionally more instances of both major wound and later joint sepsis in the rheumatoid group. For major wound sepsis the figures were 21/1369 against 43/6683, a simple uncorrected incidence ratio of 2·38 with 95% confidence limits of 4·0–1·4, and for confirmed joint sepsis 20/1369 as compared with 66/6683, an uncorrected incidence ratio of 1·48 with 95% confidence limits of 2·4–0·9. All the above figures are consistent with a risk of joint sepsis in the patient with rheumatoid arthritis, about double that for patients with simple osteoarthritis and it is a reflexion of the statistical difficulties associated with studies of this kind that even a risk ratio as high as 2:1 should be difficult to establish or refute unequivocally.

Regression analysis (see appendix) was applied to the data in an attempt to make allowance for uncontrolled factors, especially differences between hospitals. The reductions in sepsis associated with operating in ultraclean air and the differences between the outcome according to the type of joint disease or the joint operated on were similar, when assessed in this way, to the values reported above. The reduction in joint sepsis consequent upon the use of prophylactic antibiotics was 1:2·5 appreciably less than that of 1:4·0 derived from the simple comparison of sepsis incidence between those patients receiving and those not receiving such treatment. This value will, to a large extent, be determined by the data obtained from the minority of five hospitals where prophylactic antibiotics were or were not given to comparable numbers of patients and is, not surprisingly, similar to the value deduced by direct comparison of the apparent effect of perioperative antibiotics at those hospitals (Lidwell *et al.* 1982). The proportion of patients given antibiotics at these hospitals could have arisen either as a consequence of differences in the practice of individual surgeons, i.e. some administering them to most of their patients, while others rarely used them, or from some general policy which restricted the use of antibiotics to a selection of patients. When the usage of the individual surgeons at the five hospitals was examined it was clear that while some fell into the first category, i.e. very high or very low usage, the majority employed some selection criteria. Nearly two-thirds (1431/2178) of the operations at these hospitals were done by surgeons who gave perioperative antibiotics to between 20 % and 80 % of their patients. This contrasts strikingly with the practice of the other 14 hospitals, at 10 of which antibiotics were given to more than 85 % of patients and at four to fewer than 20 %. At these hospitals less than 4 % of operations, 233/5874, were done by surgeons who gave perioperative antibiotics to between 20 % and 80 % of their patients. The patients receiving perioperative antibiotics at the five hospitals were, therefore, largely a selected group and it seems most probable that the basis for selection included a belief that they were more likely to become infected. To the extent to which selection on this basis was effective, the apparent effect at these hospitals of prophylactic antibiotics will have been less than their actual value. A fully controlled French study (Hill *et al*, 1981) has reported a ratio of 1:3·5. They used cefazolin and our data reported elsewhere (Lidwell *et al*. 1983*a*) suggests that such wide spectrum antibiotics should be more effective than cloxacillin or flucloxacillin alone; these were the antibiotics used for about half of our patients who received antibiotics prophylactically. It seems, therefore, that the effective use of perioperative antibiotics can be expected to reduce the incidence of deep joint sepsis after total joint replacement to between one-third and one-quarter of that likely to occur without antibiotic.

The study design and the resulting data do not allow for any confident answers to the effects on infection of the many variations in operating procedures. Because the likely difference associated with any one of them is small, the problems associated with the confirmation or negation of any clinical benefit are formidable (Lidwell, 1982) and surgical practice must continue to be guided by judgement based on the best available bacteriological and physical understanding of the situation. The analysis, however, showed that the outcome of the operation improved generally over the period of the study and that the risk of joint sepsis was greater for those patients from whom comparatively larger numbers of bacteria had been isolated in wound samples.

When there are several methods available for reducing the incidence of sepsis, it is important to consider the results of combining them. In Table 1, this has been done for the effects of ultraclean air, special clothing and prophylactic antibiotics. The most probable interpretation of the data is that these combine multiplicatively. From the data of that table, and a knowledge of the costs of implementing any procedure, it is possible to deduce a cost-benefit, i.e. the cost per infection prevented. This can then be compared with the costs of an infection. This has been attempted by Lidwell (1984). While the use of perioperative antibiotics is, by a long way, the most cost-effective single measure, the further reductions in the incidence of sepsis obtained by operating in ultraclean air when antibiotics are used are also cost-effective. In spite of the uncertainties in the calculations, not least in the likely rates for joint failure due to sepsis, all the figures suggest that the reduction of sepsis after total joint replacement by any and all the measures discussed is, on economical ground alone, a worthwhile procedure.

APPENDIX: MULTI-REGRESSION ANALYSIS

In addition to the factors discussed in the main body of this paper, many other data were recorded, including details of operating-room practice, which might have influenced the outcome of the operation. As has already been explained, the study was not designed to explore the possible role of these factors which were only recorded to ensure that there was no significant imbalance in any of them between operations carried out in ultraclean air or in conventionally ventilated operating rooms, the control series. Any examination of the possible effect of other factors is, therefore, confounded with differences related to individual hospitals and surgeons. Furthermore, for most outcomes, including especially those involving infection, the instances were relatively few. Statistically significant effects could, therefore, only be demonstrated when these were substantial.

The simple forms of analysis used earlier become impracticable when there are many intercorrelated variables and a high degree of confounding; to allow, as far as possible, for the interaction between factors the data were analysed by employing a sequential multiple logistic regression programme (S.A.S.). A list of the factors so examined is given in Table 11.

Two of these, 'epoch' and 'wound washout', need some explanation.

Epoch. As the several hospitals did not enter the trial simultaneously their proportionate contribution varied over the period of the study. Any direct attempt to evaluate changes with time could therefore be biased by this. The term 'epoch' is used to describe the yearly sequence at each hospital, i.e. the first year at any hospital is year one by epoch, whatever the calendar date.

Wound washout. The numbers of bacteria isolated from wound washout samples varied very widely between hospitals (Lidwell *et al.* 1983*b*) and a large part of this variation seemed to be due to differing efficiencies in the way the sampling was done. Direct comparison between operation outcome and the numbers isolated from washout samples is, therefore, not useful because the higher counts will simply be those from those hospitals where the procedure was most efficient. The sample values at each hospital have been split into three and comparison made between the outcome of operations where the sample values lay in the upper, middle and lowest third of values.

The basic statistical model was

$$\ln P/(1-P) = a+b_1x_1+b_2x_2+\ldots,$$

where P is the probability of a defined outcome, a is a constant, and b_1, b_2, etc., are the coefficients associated with values x_1, x_2, etc., of factors 1, 2, etc. All but one of the factors examined were non-numeric dichotomies so that the corresponding x takes the value 1 or 0 according to the presence of absence of that factor. Only in the case of epoch was this treated as a semi-continuous variable with values 1, 2, 3.

As P is small the regression can be written as:

$$P \simeq a'b'^{x1}_1\, b_2'^{x2}\, b_3'^{x3}\ldots,\text{where } a' = e^a,\ b'_1 = e^{b_1}, \text{ etc.}$$

In this formulation coefficients greater than 1 indicate a proportionate increase in the probability of the outcome in the presence of the factor, i.e. a coefficient

Table 11. *Factors examined by a sequential regression analysis (with number of patients)*

Hospitals	Nineteen hospitals included as independent variates.
Epoch	Years 1, 2 and 3 (where operations recorded at any hospital extended over more than three years, the additional numbers were added to either the first or the third year as convenient)
Ventilation	(1) Ultraclean air with conventional clothing (1789) (2) Ultraclean air with body-exhaust suits or plastic patient isolator (2134)
Antibiotics	(1) Given prophylactically perioperatively (5831) (2) Incorporated in the cement (484) (3) Course extended beyond seventh post-operative day (3505). (4) Group 1 antibiotics; cloxacillin, flucloxacillin and equivalent (2665) (5) Group 2 antibiotics; Group 1 with ampicillin, a cephalosporin, gentamicin in the cement (2523)
Age	Over 55 at time of operation (4200)
Sex	Male (2892)
Joint operated	Knee (1270)
Diagnosis	Rheumatoid (1369), osteoarthritis (5962)
Steroids	Administered (482)
Previous operation	On same site (729)
Sepsis existing	Immediately before operation (46)
Carrier of *Staph. aureus*	1555, out of 4767 examined
Patient skin preparation	Chlorhexidine in alcohol (3157), any form of iodine (2930)
Surgeon's scrub	Chlorhexidine with detergent (2568), iodine with detergent (1264), chlorhexidine and iodine with detergent (2385)
Drapes	Non-adhesive (1876)
Wound rinse	Containing antibiotic (3664)
Incision (hip)	Anterolateral (1698), posterior (936), (remainder, 98% lateral)
Great trochanter (hip)	Detached (3136)
Cement	CMW (6107)
Wound washout	(1) Count in upper third for hospital, 1084 out of 3587. (2) *Staph. aureus* isolated (62)
Duration of operation	Longer than 2 h (2564)
Anticoagulants	Given in 901 operations
Duration of follow-up	Up to 1 year (2585), one to 2 years (2088)

of 2, a twofold increase, and coefficients less than 1 a proportionate decrease. The sequential analysis introduces factors into the regression so long as the regression coefficient then obtained is significant at a previously determined level, e.g. 0·05, 0·01, etc. In order to make the maximum allowance for inter-hospital variation the programme was first run including the 19 hospitals, together with length of follow-up for longer-term outcomes, as the only variates. Any of these which contributed significantly to the variation for a particular outcome were then included, without possibility of removal, in a further sequential regression analysis with the factors listed in Table 11.

The coefficients derived in this way for the 17 factors that gave significant values are shown in Table 12 for the nine outcomes of most interest. In addition, significant coefficients were found for six hospitals, ranging from 4 to 16, for confirmed joint sepsis; for eight hospitals, with coefficients from 0·27 to 15, for suspected joint sepsis; for nine, with coefficients from 0·25 to 3·0, for re-operation without evidence of sepsis; and for six, with coefficients from 0·14 to 2·5 for major wound sepsis.

In our previous papers and the preceding sections of this, the effects of ultraclean air and of perioperative antibiotics have been expressed in terms of the ratios of the incidence in the control group, conventional ventilation or no prophylactic antibiotics given, to that when the operation was done in ultraclean air or with prophylactic antibiotics. The regression coefficients derived above give the probability ratios to the control group, i.e. the reciprocal of the incidence ratios used previously. The values of the incidence ratios deduced for these factors have therefore been included in Table 12, in addition to the regression coefficients, in order to facilitate comparison with earlier figures.

The incidence ratios derived from the regression analysis for the effect of ultraclean air on joint sepsis (1·82 with conventional clothing and 4·55 with body-exhaust suits or an isolator) are very close to those already deduced (Table 1) for the effect of ultraclean air and confirm that there was no appreciable imbalance in respect of any significant factors between the control and ultraclean air groups.

The coefficients for the prophylactic use of antibiotics confirm the substantially lower incidence of all kinds of sepsis when these were given perioperatively.

Prolonged antibiotic therapy, beyond the eighth day after operation, was associated with a greater incidence of wound and of joint sepsis but was more likely to have followed signs of sepsis than to have led to it. When the factor for prolonged therapy is excluded from the analysis the incidence ratio for confirmed sepsis without prophylactic antibiotics compared with that when these were given is 2·5. This value is appreciably less than that of 4·0 derived from the data by direct comparison without any allowance for possible hospital or surgeon differences (Lidwell *et al.* 1982) and virtually identical with that deduced in that paper from the results at the minority of hospitals where comparable numbers of patients received or did not receive perioperative antibiotics.

We have already reported (Lidwell *et al.* 1983*a*) that the use of cloxacillin or flucloxacillin alone did not appear to affect the incidence of joint sepsis associated with intestinal-type organisms but that this was reduced, or eliminated, when wide spectrum antibiotics were given, i.e. the above with ampicillin, gentamicin or a cephalosporin. Which of these two types of antibiotic prophylaxis was used is almost wholly associated with the hospital in which the operation was performed; it is therefore impossible to derive from the data any meaningful figures for their relative value in reducing joint sepsis overall or for any other operation sequela.

The coefficients for operations on the knee and for patients with rheumatoid arthritis confirm the analyses already given, with a much higher (greater than twofold) incidence of major wound sepsis among patients with rheumatoid arthritis than for other diagnoses. There were no significant coefficients associated with the administration of steroids.

Table 12. *Regression analysis*

Factor	Joint: Con-firmed sepsis	Joint: Sus-pected sepsis	Joint: Reop-eration, no sepsis	Wound: Major sepsis	Wound: Possible or minor sepsis*	Pain, Inpatient: Non-weight	Pain, Inpatient: Weight	Pain, Outpatient: Non-weight	Pain, Outpatient: Weight
	Proportionate coefficients for								
Number of patients	86	85	244	64	565	201	92	369	714
With significant coefficients									
Ultraclean air†									
Conventional pattern clothing	0·55/1·82	(÷8)	—	(÷8)	—	—	—	(+6)	—
Body-exhaust or isolator	0·22/4·55	0·41/2·44	—	0·25/4·00	(+9)	—	—	—	—
Prophylactic antibiotics†	0·17/5·88	0·50/2·00	—	0·20/5·00	0·45/2·22	—	0·37/2·70	—	—
Antibiotic in cement	—	—	2·01	—	3·67	—	—	—	—
Antibiotics for 9 days or more	3·32	—	—	3·00	2·72	—	3·67	—	—
Age: over 65 years	—	—	—	—	1·22	—	—	—	(+3)
Knee-joint replacement	—	2·23	2·72	—	1·49	2·46	2·72	2·22	2·72
Rheumatoid	—	—	—	2·22	—	—	—	—	0·61
Osteoarthritis	—	—	—	—	(+4)	(+9)	—	1·65	—
Previous operation on site	—	—	(+10)	—	—	1·65	—	1·65	1·65
Existing sepsis	6·05	—	—	—	—	—	—	—	—
SA in wash-out	7·39	—	—	5·47	—	—	—	—	—
Wash-out count upper third	1·82	—	—	—	—	—	—	—	—
CMW cement	(÷9)	(÷9)	—	0·50	—	—	—	—	—
Detached trochanter	—	3·00	—	—	—	—	—	—	—
Pre-op scrub, chlorhexidine in detergent	—	—	—	—	—	(+9)	3·00	—	—
Epoch, 1st, 2nd, 3rd hospital year,/year	0·61	—	0·74	—	—	0·82	0·61	0·74	0·82
Variance absorbed, %	2	2	2	1	4	4	2	3	7

The coefficients given are significant at the 5% level, except for the columns marked *, when the number of positive events exceeded 300 and the significance level has been lowered to 1%. The numbers in parentheses give the significance level, %, at which that factor would enter the regression; + with a coefficient > 1, ÷ with a coefficient < 1. —, an entry level above 10%.

† For 'ultraclean air' and 'prophylactic antibiotics' the reciprocals of the regression coefficients have been given after the solidus, /. These values correspond to the incidence ratios given in Tables 4–6, and in earlier papers, for the ratios of the incidence under 'control' conditions (conventional ventilation and clothing or prophylactic antibiotics not given) to the incidence with the specified condition.

Neither age nor sex showed any appreciable relationship to the operation outcome.

A previous operation on the site was not associated with any significant differences in the incidence of sepsis although there was a moderately higher incidence of abnormal pain, both during the inpatient period and after discharge from hospital.

Sepsis existing immediately prior to operation and isolation of *Staph. aureus* from the wound washout were both associated with large positive regression coefficients on joint sepsis, with increased risks of more than six- and sevenfold respectively, but the numbers were very small – only two and five cases of joint sepsis respectively.

When the bacterial count from the wound washout sample was in the highest third of sample values at the hospital concerned the risk of subsequent joint sepsis was nearly twice that among all the other patients.

Antibiotic in the cement appeared to be related to a higher incidence of re-operation not associated with infection and with more minor sepsis. But these results came almost entirely from only two hospitals. CMW cement was associated with rather less major wound sepsis than others. The higher incidence of suspected joint sepsis after operation during which the greater trochanter was detached could well be due to the association of pain with this procedure, often the only reported abnormal sign and frequently due to fracture of the re-attachment wires.

Anticoagulants, predominantly warfarin, were given perioperatively in any significant numbers at only four hospitals (845 of 1911 patients). Records were not made of the incidence of venous embolism. The number of deaths, after insertion of a prosthesis, reported from these hospitals during the period of follow-up among those who received anticoagulant was 21, including five as a result of pulmonary embolism in the immediate post-operative period. Among the patients who did not receive anticoagulants there were 31 deaths with only one, or possibly two, from pulmonary embolism. These numbers are very small, with a higher incidence of death from pulmonary embolism among those patients who received anticoagulants 5/845 = 0·59 % compared with 1 or 2/1066 = 0·09 % or 0·19 % among those who did not, but there may well have been selection of patients with respect to the anticipated risk.

Different antibacterial skin treatments, whether for patient or by the surgeon, the use of adhesive drapes, the type of incision (for hips), the wound rinse, the duration of the operation did not appear to have had any influence on the operation outcome within the rather wide limits of demonstrable values.

There is within the data evidence of improvement during the three years of observation at each hospital, in respect of joint sepsis, the incidence of re-operation without infection and of all kinds of pain. The magnitude of the effect is quite considerable: the yearly coefficients range from 0·6 to 0·8, corresponding to an average fall of nearly 50 % from the first to the third year. Such a rate of improvement could hardly be sustained, it would correspond to a reduction of around tenfold if continued up to the present time (1983). There was an increase from 67 % to 75 % in the proportion of patients given perioperative antibiotics between the first and third year but this would account for an annual reduction in joint sepsis of only about 10 % and would not be expected to have any influence on the incidence of re-operation without infection. In the case of confirmed joint sepsis, the fall in incidence with epoch is largely determined by the figures from two hospitals. These hospitals accounted for no more than 13 % of the operation but contributed 45 % of the instances of confirmed joint sepsis and over 80 % of the reduction in incidence between epochs 1 and 3. No such association with a few hospitals is, however, apparent for any other outcome.

The results of this regression analysis, for the reasons given earlier, must be interpreted with caution. In such a large body of data, within which several hundred comparisons may be made, an appreciable number of apparent differences, significant at the 0·05 level, must be expected from the operation of random influences alone.

The hospitals that contributed to the data presented here and in the earlier papers describing the investigation were: Aberdeen Royal Infirmary; Academic Hospital, Uppsala; Bethnal Green Hospital, London; Chester City Hospital, Chester; Gartnavel General Hospital, Glasgow; Harlow Wood Orthopaedic Hospital, Nottingham; Huddinge Hospital, Stockholm; The London Hospital; Malmö General Hospital, Malmö; Northern General Hospital, Sheffield; Northwick Park Hospital, Harrow, Middlesex; The Nuffield Orthopaedic Centre, Oxford; the Princess Margaret Rose Orthopaedic Hospital, Edinburgh; the Royal Orthopaedic Hospital, Birmingham; The Royal Postgraduate Medical School, Hammersmith; The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire; St. Thomas's Hospital, London; Stracathro Hospital, Brechin; and the University Hospital, Lund. We acknowledge with gratitude the collaboration of the several hundred surgeons, microbiologists, operating-room staff, recording nurses and others without whose help it could not have been carried through.

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