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Pre-operative asymptomatic bacteriuria: a risk factor for prosthetic joint infection?

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SUMMARY

Background: Infection is a rare complication following implantation of prosthetic material into a joint. The impact of asymptomatic bacteriuria (ASB) before elective operations and the subsequent risk of prosthetic joint infection (PJI) are not well understood.
Aims: To assess the prevalence of ASB amongst patients undergoing total arthroplasty of the hip and knee; and to determine the rates of PJI diagnosed within two years of the arthroplasty and if ASB is an independent risk factor for developing PJI.
Methods: Patients who had total/unicondylar knee or total hip arthroplasty were reviewed retrospectively over a five-year period. Pre-operative urine samples within one year of surgery were analysed, and those with ASB were identified. The primary outcome was PJI within the first postoperative year.
Findings: In total, 5542 patients were included. Of these, 4368 had a pre-operative urine culture recorded. The prevalence of ASB was 140 of 4368 (3.2%). The overall PJI rate was 56 of 5542 (1.01%). Of those with PJI, 33 had a pre-operative urine sample recorded. The infection rates were 5% (seven of 140) in the ASB group, 0.61% (26 of 4228) in the no-ASB group and 1.96% (23 of 1174) in the group without a urine sample ($P < 0.001$). The ASB isolate was the same micro-organism as the PJI isolate in one of the seven cases.
Conclusion: The association between ASB and PJI is statistically significant, but the urine isolates did not relate to the isolates in the prosthetic joint, suggesting that the relationship is unlikely to be causal.

Introduction

With an ageing, co-morbid population, rates of joint replacement are increasing. Prosthetic joint infection (PJI) is a rare but serious complication of arthroplasty, with the infected prosthesis often requiring debridement and/or revision. This comes at great expense to the patient's quality of life and the healthcare economy. An expansive campaign to reduce PJI has led to the introduction of laminar airflow systems in operating theatres, stringent sterilization of orthopaedic equipment, and diligent postoperative wound care. Despite this focus on controlling extrinsic sources of infection, it is widely established that the majority of these infections are intrinsic, from the patient's own flora.

One possible source of infection is urinary tract colonization in patients with asymptomatic bacteriuria (ASB). ASB has been implicated as a cause of PJI despite debatable evidence, and significant variations in diagnostic and management practices. UK guidance recommends routine urinalysis at pre-assessment, but does not stipulate how ASB should be managed [1]. Spanish

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guidelines advocate treatment of ASB pre-arthroplasty [2], while Australian guidance does not recommend this practice [3].

In 2014, a three-centre study from the UK, Portugal and Spain concluded that ASB was an independent risk factor for PJI, particularly those caused by Gram-negative bacteria, despite reported differences between organisms isolated from pre-operative urine samples and subsequent postoperative wound cultures [4]. Also, in this study, there was no randomization to treatment, but subanalysis of the study population on the effect of antibiotic treatment of ASB showed no significant difference between the treated group and those who were not treated with regard to risk of PJI. More recent reviews of evidence cast doubt on the benefit and cost-effectiveness of this practice [5]. In the UK, it is common practice for patients undergoing elective arthroplasty to have pre-operative urine screening for bacteriuria. If positive, even in the absence of symptoms, the patient is treated with antibiotics. Anecdotally, operations have been postponed or cancelled for this reason.

The aims of this study were:

- to assess the prevalence of ASB amongst patients undergoing total arthroplasty of the hip and knee;
- to determine the rates of PJI diagnosed within two years of the arthroplasty, and if ASB is an independent risk factor for developing PJI;
- to analyse and categorize the timeline of subsequent PJI into early, delayed and late, as per the MSIS classification [6], which is a unique feature of this study; and
- to provide guidance to the hospital on areas where pre-operative screening should be concentrated.

To the authors' knowledge, this is the first UK published report on these issues.

Materials and methods

Patients who had primary or revision total/unicondylar knee or primary or revision total hip athroplasty at Basingstoke Hospital, UK between 1st January 2011 and 1st January 2014 were reviewed retrospectively, and the operation date was noted. Pre-operative urine results reported within one year before surgery were analysed, and those with ASB were identified.

Pre-operative urine analysis forms part of the pre-operative assessment at the study institution. ASB was defined as the isolation of $>10^5$ colony-forming units/mL in the absence of symptoms or signs of urinary tract infection. All positive ASB in this study were treated according to the antibiotic sensitivity profile.

The primary outcome in this study was prosthetic joint infection within the first postoperative year. The secondary outcome was late prosthetic joint infection from 12 to 24 months after surgery. A PJI in this study was defined in accordance with the criteria of Atkins *et al.* [7] for microbiological diagnosis of PJI (i.e. two or more positive cultures from deep samples with the same organism, regarded as clinically significant and treated with antibiotics). For the latter, clinic letters were reviewed. Samples from infected arthroplasty included in this study were all cultured directly on to standard media as well as an enrichment broth. The enrichment broth was subcultured after seven days of incubation.

From January 2011 to 31st December 2016, all patients who had bone/tissue/fluid samples cultured and registered in the microbiology database at Hampshire Hospitals NHS Foundation Trust, UK were extracted from the hospital's microbiology electronic database. In order to filter through the superficial samples, such as swabs and samples from septic arthritis as opposed to PJI, this list of microbiological cultures was overlapped with a prosthetic joint registry held at the orthopaedic department as an accurate record of all prosthetic joint operations. Patients' operative and clinic records were retrieved and analysed to ensure that positive samples were clinically correlated and managed as an infection, and not regarded as a contaminant (based on International Consensus on Periprosthetic Joint Infection or MSIS [6]). All patients treated for PJI were included. Each PJI was then classified as early, delayed or late according to the MSIS criteria (within three months, six months and >12 months of surgery). Pre-operative urine cultures were assessed in all patients included in the study. ASB was defined as the isolation of $>10^5$ colony-forming units/mL in the absence of symptoms or signs of urinary tract infection.

A retrospective analysis was performed to assess corroboration of pre-operative urine cultures with subsequent PJI up to two years following surgery.

Results

In total, 5542 patients were included during the study period, of whom 4368 had pre-operative urine samples on record. The average age at the time of surgery was 68 years. A similar proportion underwent total hip arthroplasty ($N = 2766$) and total/unicondylar knee arthroplasty ($N = 2776$). Of these, 3328 (60%) were women and 2214 (40%) were men.

In total, 56 of 5542 (1.01%) patients were diagnosed and treated for PJI. Fifty of these (89.3%) were due to Gram-positive bacteria and six (10.7%) were due to Gram-negative bacteria. Over one-third of these infections (20/56, 35.7%) were due to meticillin-susceptible *Staphylococcus aureus* (MSSA), as shown in Table I.

Of the 5542 patients included, 1174 (21.2%) did not have a pre-operative urine culture on record. The other 4368 (78.8%) patients had a pre-operative urine culture on record within a year before the date of surgery, of which 140 (3.2%) had pre-operative ASB.

The micro-organisms isolated from pre-operative urine cultures were mainly Gram-negative bacteria (123 of 140, 87.7%) and only one sample grew MSSA (0.7%) (Table II). The infection rate in the ASB group was 5% (seven of 140), which was significantly higher than the rates in the no-ASB group (0.61%, 26 of 4228) and the group without a screening urine sample (1.96%, 23 of 1174) ($P < 0.001$ using Chi-squared test).

The ASB group had a higher proportion of PJI due to Gram-negative bacteria (28.57%, two of seven) compared with the no-ASB group (7.69%, two of 26) and the group without a screening urine sample (8.70%, two of 23), although this was not statistically significant ($P = 0.262$) and numbers were small. The ASB isolate was the same micro-organism as the PJI isolate in one of the seven cases.

Table III shows the overall summary of isolated micro-organisms in relation to ASB.

Table I shows the breakdown of species of micro-organisms isolated from PJI in relation to the type of PJI surgery. A

Table I
Micro-organisms isolated from prosthetic joint infections (PJI) in relation to the type of surgery and the time of PJI

Isolated micro-organisms	Overall ($N = 56$)	Late	Hip	Knee	ASB	No-ASB	No urine test available	Early	Delayed	Late
Gram-positive	50									
Coagulase-negative staphylococci	22	8	15	7	3	10	9	9	5	8
Meticillin-susceptible *Staphylococcus aureus*	20	8	7	13	1	12	7	9	3	8
Group B streptococcus	3	3	–	3	–	–	3	–	–	3
Group C streptococcus	1	–	–	1	0	1	–	1	–	–
Enterococcus spp.	1	–	1	–	0	–	1	1	–	–
Group A streptococcus	3	1	1	2	1	1	1	1	1	1
Gram-negative	6									
Escherichia coli	5	3	1	4	1	2	2	2	–	3
Klebsiella oxytoca	1	1	1	–	1	–	–	–	–	1

ASB, asymptomatic bacteriuria.

significantly higher proportion of MSSA PJI were of the knee (65%) compared with the proportion for coagulase-negative staphylococci (32%) ($P = 0.032$ using Chi-squared test). A greater proportion of coagulase-negative staphylococci caused hip PJI than MSSA (68.2% vs 35%) ($P = 0.032$, Chi-squared test). This could have implications for antibiotic prophylaxis and screening programmes. The micro-organisms isolated were also studied in relation to the timing of PJI (i.e. early, delayed or late); no significant difference in the rate of early and late PJI was found (41.1% and 42.9%, respectively), but the rate of delayed infections was significantly lower at 16.1% (Table I).

Discussion

This is the largest UK-based study addressing the issue of ASB and PJI risk to date. It included 5542 patients, which was more than twice the number of patients included in a similar study by Sousa *et al.* [4]. The present study found the PJI rate to be 1.01%, compared with 1.7% reported by Sousa *et al.* The present findings confirmed the higher rate of PJI amongst the ASB group compared with the no-ASB group (5% and 0.6%, respectively), although the rates reported by Sousa *et al.* were less divergent (4.3% and 1.4%, respectively). The present study found the overall rate of ASB to be significantly less than that reported in other studies (3%), compared with 12.1% reported by Sousa *et al.* [4].

It could be argued that, as all of the ASB patients in the present study had received treatment, this may have influenced the rate of PJI in this group (i.e. more patients might have developed PJI if not for screening and treatment). However, the group without urine samples is likely to represent a mixed population in relation to ASB, and their infection rate is likely to represent rates of PJI when screening and treatment is not undertaken. Also, the effect of antibiotic treatment of ASB prior to arthroplasty has not been shown to influence the risk of PJI in similar studies [5].

These findings clearly demonstrated the dominance of Gram-positive organisms as a cause of PJI (89%) at the study institution, with evidence of MSSA predilection for knee arthroplasty and coagulase-negative staphylococci for hip arthroplasty. Both are skin-colonizing micro-organisms, and interventions to reduce the risk of PJI should focus on reducing the bio-burden of these organisms instead of Gram-negative organisms from the urine. The difference in micro-organisms causing hip and knee infections can help guide antibiotic prophylaxis protocols, screening and bioburden reduction strategies.

The effects of urinary tract conditions that are associated with increased risk and frequency of urinary tract infections

Table II
Micro-organisms isolated from pre-operative urine cultures

Micro-organism	*N* (%) of isolates
Gram-negative	
Escherichia coli	115 (82.1)
Pseudomonas aeruginosa	5 (3.5)
Proteus spp.	3 (2.1)
Gram-positive	
Enterococcus spp.	11 (7.8)
Coagulase-negative staphylococci	5 (3.6)
Meticillin-susceptible *Staphylococcus aureus*	1 (0.7)
Total	140

Table III
Micro-organisms isolated from prosthetic joint infections (PJI) in relation to asymptomatic bacteriuria (ASB)

Patient	ASB micro-organism	E/D/L	Site	PJI micro-organism
1	*Escherichia coli*	D	Hip	Coagulase-negative staphylococci
2	*Enterococcus faecalis*	D	Knee	Group A streptococcus
3	*E. coli*	D	Hip	Meticillin-susceptible *Staphylococcus aureus*
4	*E. coli*	E	Hip	Coagulase-negative staphylococci
5	*E. coli*	E	Knee	*E. coli*
6	*E. coli*	D	Knee	Coagulase-negative staphylococci
7	*E. coli*	L	Hip	*Klebsiella oxytoca*

E, early; D, delayed; L, late.

(e.g. urine retention, indwelling catheters on development of PJI post-arthroplasty) are not fully understood, and in these selected cases, there might be benefits in screening for ASB and treatment prior to surgery. However, this is likely to be short term and therefore might only influence the rate of early PJI.

This study showed no correlation between ASB group and the micro-organisms isolated from the PJI samples. This confirms the findings of Sousa *et al.* [4], and includes Gram-positive and Gram-negative bacteria. The increased rate of PJI in the ASB group could be an indicator of higher bioburden amongst this group, altered host immune functions, or increased susceptibility to colonization and infection, rather than a direct cause and effect association. It could also be due to the effects of antibiotic treatment altering resident flora, and predisposing these patients to infection with different and possibly more resistant micro-organisms or ones with a different susceptibility profile. Further studies are needed to explore these findings.

This study showed lower prevalence of ASB compared with rates reported in the literature amongst similar patient cohorts and the general population (4—19%) [4,6,7]; it is not clear why this was the case. Further studies of the prevalence of ASB in the general population in the study area might help explain the low prevalence in the study cohort.

There was no significant difference in the rates of early and late PJI (41.1% and 42.9%, respectively) in this study, but the rate of delayed infections was significantly lower (16.1%). This is in keeping with the published literature [8]. The present study did not show any differences in the association between ASB and PJI in any of these three subgroups, which suggests that the perceived association of ASB with early PJI is unfounded.

A recent position paper of the expert group 'Infection of Swissorthopaedics' [9] concluded that ASB is common, and studies conducted since 2013 failed to show a direct link between treatment of ASB and reduced risk of PJI or vice versa. They noted that these studies showed that different micro-organisms were isolated from the urine to those isolated from PJI. They concluded by recommending that urine screening for bacteriuria in asymptomatic patients undergoing orthopaedic implant surgery should be avoided because antibiotic treatment of ASB does not prevent joint infections, and is associated with adverse events, costs and development of antibiotic resistance [10].

This study analysed single urine samples collected at pre-assessment, and did not include further analysis of treatment in the ASB group. This was because the study was focused on investigating the link between ASB and subsequent PJI, and a third comparator arm existed as the group of patients who did not have pre-operative urine samples. The rate of PJI amongst this group was found to be significantly less than in the ASB group.

This was a single-centre retrospective study. It included a large sample with three comparator arms, and included data covering a five-year period.

In conclusion, this large study showed a low prevalence rate of 3.2% of ASB amongst patients screened before arthroplasty procedures at the study institution. Although the rate of PJI was significantly higher in the ASB group, there was no evidence of a direct link as the micro-organisms isolated did not correlate. This discordance suggests that efforts to reduce PJI caused by Gram-positive bacteria are likely to be more effective than screening for ASB. To this end, the difference in the predominant Gram-positive bacteria causing infection in hip and knee PJI might suggest that different antibiotic prophylaxis and prevention strategies may be required for different types of prosthetic joint surgery.

Conflict of interest statement
None declared.

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