Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 14 December 2011, doi:10.4414/smw.2011.13306
Cite this as: Swiss Med Wkly. 2011;141:w13306

No need to search for the source of haematogenous arthroplasty infections

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Summary

QUESTIONS UNDER STUDY/PRINCIPLES: Prosthetic joint infections (PJI) may be a potential sentinel event for an unknown neoplastic or infectious source in elderly patients. However, the value and cost-effectiveness of investigations to determine the origin of these infections is unknown.

METHODS: Retrospective study at Geneva University Hospitals, evaluating associated medical examinations performed in search of the origin of all presumed surgical site and haematogenous arthroplasty infections.

RESULTS: A total of 182 PJI were found in 182 patients (median age 75 years). Seventy PJI (38%) were classified as probably haematogenous, occurring more than 2 years post-implantation, with 27 (15%) due to Gram-negative pathogens. Overall, the origin of PJI was found solely by admission history in 28 cases (15%). Among the remaining 154 cases, no remote origin could be detected despite 17 echocardiograms, 17 other sonograms, 49 chest x-rays, 23 computed tomograms, 107 urinary cultures, 11 endoscopies, 9 scintigraphies and 31 medical specialist consultations. The average cost of these exams was 675 Swiss francs (845 US$) per PJI. At long-term follow-up six patients were found to have developed a neoplasm, of which only one (hepatocellular carcinoma after PJI due to *Streptococcus bovis*) could eventually be attributed to prior infection.

CONCLUSIONS: From an epidemiologic point of view, patient history is the best way to predict the origin of PJI. Blind additional radiographic or endoscopic exams are costly, inconclusive and do not contribute to the management of these cases.

Key words: *haematogenous infection; arthroplasty; origin; radiology; endoscopy*

Introduction

Most prosthetic joint infections (PJI) are felt to be acquired in the operating theatre during implantation, but the exact proportion of PJI acquired in the operating theatre rather than acquired afterwards is unknown [1, 2]. A minority of PJI (10–25%) are believed to be haematogenous from a remote source that may either be obvious or occult.

With the availability of sophisticated radiological techniques and various endoscopic procedures in most resource-rich countries, many physicians perform additional examinations, even in the absence of a history supporting PJI. The rationale is to exclude an underlying cancer or occult abscess that could theoretically relapse following treatment. However, the scientific evidence for this attitude does not exist, with the sole exception of PJI due to *Streptococcus bovis* that might be associated with colon lesions [3].

With the objective of reducing costs and avoiding exposure to unnecessary radiation and examinations, we assessed the origins of our patients with PJIs in order to compare the performance of a careful and cost-free history versus relatively expensive radiological and endoscopic techniques in predicting the origin of the infection.

Methods

Setting

The Geneva University Hospitals is a 2,200-bed tertiary teaching hospital and the only public hospital in the canton (county). The Orthopaedic Service has conducted an arthroplasty cohort since 1996, and engaged a dedicated Infectious Diseases (ID) physician since 2000 [4]. In addition to patients operated upon at our hospital, many PJIs in patients operated upon elsewhere are referred to our institution for treatment and are documented in a separate, septic cohort.

Data collection and definitions

The diagnosis of PJI was based upon the presence of intraoperative pus together with clinical signs of infection (new onset of pain, fever, sinus tract, discharge) or radiographic signs of prosthesis loosening. Identification of the infecting organism required the same pathogen to be present in at least two intraoperative samples.

An orthopaedic surgeon (CB) and an ID physician (IU) retrospectively collected 43 variables per case from archived and electronic databases from February 1996 to June 2011. Only the first episode of PJI of an individual patient was assessed, and other orthopaedic implant infections besides prosthetic joints were excluded. In addition to standard variables for PJI (demographic information, pathogens, surgical and antibiotic treatments), we focused particular interest on the first date when PJI origin was noted in the medical file. Medical examinations performed in the setting of a positive history (e.g., chest radiograph on clinical auscultation of pneumonia) were not interpreted as "additional examinations". Likewise, examinations performed for other reasons unrelated to PJI, such as mammography in women or gastroscopy for cirrhotic patients, were not considered "additional examinations" for PJI and were also excluded from the analysis. Finally, data sampled during the last visit for any medical problem at our hospital ensured the long term follow-up and reported on the underlying diseases missed during the first hospitalisation for PJI. The local Ethics Committee supports the arthroplasty cohort and the clinical follow-up of other patients.

Results

PJI and study population

A total of 182 PJI (89 total hip arthroplasties, 21 medullar hemiarthroplasties, 68 total knee replacements, 2 total ankle replacements, 1each of total elbow and total shoulder arthroplasties) were retrieved among 182 patients (92 females; 51%) (table 1). Their median age was 75 years, with a range from 31–97 years. Eighty-one patients (45%) had diseases or medication potentially associated with immunosuppression: diabetes mellitus (n = 30), daily dependency on alcohol (n = 14), chronic renal insufficiency (n = 9), autoimmune disease requiring steroids (n = 8), cirrhosis CHILD C (n = 7), and HIV disease (n = 1). Sixteen patients had an active or previous neoplasm in the preceding five years. Four patients had multiple origins for immune suppression.

The median delay between arthroplasty and first clinical signs of PJI was 1 year, with a range from 5 days–27 years. Overall, 56 (31%) of PJI occurred after a delay of 3 months following prosthesis insertion. 56 (31%) occurred between 3 months and 2 years, and 70 (38%) were classified as probably haematogenous, occurring after 2 years post-arthroplasty according to the criteria of Zimmerli et al. [2]. The pathogens responsible for PJI varied considerably (table 2). We failed to detect an outbreak situation. 37 episodes (20%) were bacteraemic with the same pathogen as retrieved from intraoperative samples. In 10 episodes (5%), the pathogens could not be identified. The proportion of Gram-negative PJI was significantly higher after 2 years compared to Gram-positive infection (tables 1 and 2).

All PJI were treated with antibiotics for a median duration of 7 weeks (range 3–15 weeks) and underwent surgery for curative purposes.

Origins of PJI

Positive history

Overall, the origin of PJI was determined by history in 28 cases (15%) because patients reported clinical signs of a recent or active remote infection, including urinary tract infections (n = 9, of which 2 were chronic prostatitis), coetaneous infections (n = 6, of which two were secondary to animal bites and one a foot ulcer), gastrointestinal infections (n = 6, of which there were 2 cholecystitis, three colitis and 1 diverticulitis), endocarditis (n = 3), pneumonia (n = 2), central venous line infection (n = 1), and 1 Pseudomonas infection in a patient with sickle cell anaemia. The median delay between admission and the first notification of the origin of PJI in the medical record was 0.5 days, with a range from 0–10 days. The interpretation was correct from the start, and there were no first-time errors in diagnosis.

Table 1: Gram-positive versus Gram-negative prosthetic joint infections.

	Gram-positive n = 145	**Gram-negative n = 27**	**p value***
Patients			
Female gender	70 (48%)	15 (56%)	ns
Median age	75 years	76 years	ns
Immunosuppressed patients±	63 (43%)	14 (52%)	ns
– Active cancer	14 (10%)	0 (0%)	ns
– Chronic alcoholism	9 (6%)	4 (15%)	ns
Infections			
Early infections (0–3 months)	47 (32%)	8 (30%)	ns
Late infections (>2 years)	50 (34%)	16 (60%)	0.02
Documented bacteraemia	29 (20%)	8 (30%)	ns
Knee joint prosthetic infections	49 (34%)	11 (41%)	ns
Detected remote origin	14 (10%)	14 (52%)	<0.01
Investigations			
Radiology	62 (43%)	14 (52%)	ns
Echocardiography	17 (42%)	0 (0%)	ns
Endoscopy	6 (4%)	4 (15%)	ns
Median costs of exams	450 Swiss francs	556 Swiss francs	ns

* Pearson-χ^2, Fisher-exact or Wilcoxon-ranksum-test, as appropriate

ns = not significant (*p* value >0.05)

± One patient may have more than one type of immune suppression: diabetes, alcoholism, chronic renal insufficiency, disease requiring steroids, cirrhosis and HIV disease.

Investigations

Importantly, among the remaining 154 cases no remote origin of the infection could be detected despite additional blind, not clinically driven examinations. These included 49 chest radiographs, 4 orthopentogrammes, 17 echocardiograms, 13 abdominal and 4 genitourinary sonograms, 13 abdominal computed tomograms (CT), 6 thoracic CT, 4 thoraco-abdominal CT, 107 urinary cultures, 4 gastroscopies, 7 colonoscopies, 1 PET scan, 9 bone scintigraphies, and 31 medical specialist consultations. These cases were interpreted either as "surgical site infection" acquired during prosthetic implantation or of unknown haematogenous origin. In none of these patients was the origin of the infection revealed, nor was another site of infection found during follow-up. If the source was not clear within ten days it was never revealed during the entire study period.

Origin of infections by different subgroups

The majority of these cases without identified origin occurred within 2 years following arthroplasty, as compared to episodes with identified origins (103/154 vs. 9/28; χ^2-test, p <0.01), and were also less frequently associated with bacteraemic infection (23/154 vs. 14/28 χ^2-test, p <0.01). Furthermore, the origin was identified less often in patients with a Gram-positive infection than in those with Gram-negative PJI. Echocardiography was exclusively performed in Gram-positive PJI while endoscopy was requested in Gram-negative infections (table 1).

Follow-up

All patients were followed up (median 3 years, range 0.3–13.4 y). 20% of all episodes had a follow-up of less than one year. 41 patients died during follow-up secondary to diseases already known before the PJI episode. There were no deaths related to accidents. During follow-up, 6 patients (3%) were diagnosed with a neoplasm after a median 3.5 years (range 0.5–6 years). In the review of their medical history, only one patient with hepatocellular carcinoma was possibly linked to a prior PJI due to *S. bovis* 4 years ago (table 3). This patient had cirrhosis due to chronic alcoholism. However, we were unable to prove a direct causal relationship because the patient did not undergo endoscopic or radiological evaluation during hospitalisation for PJI. The cancer may have developed after the PJI episode, given the fact that the alcohol abuse was chronic and ongoing. The second patient with *S. bovis* PJI underwent a complete examination with colonoscopy, two abdominal CT, and echocardiography. No abdominal pathology was found during hospitalisation or during the active follow-up of two years.

Costs

As of the last study year, 2011, the fixed "blind" examination costs were as follows: chest radiogram, 106 Swiss francs (CHF); abdominal sonography, 173 CHF; echocardiography, 240 CHF; abdominal CT, 753 CHF; thoraco-abdominal CT, 1262 CHF; gastroscopy, 350 CHF; colonoscopy, 460 CHF; and urinary tract culture, 31 CHF if negative and 101 CHF if positive. Specialist medical consultations were free of charge for most patients.

Table 2: Pathogens of arthroplasty infections; above Gram-positives; beneath Gram-negatives.

Pathogens	**Acute & subacute infections**	**Late infections***
	n = 112	**n = 70**
Methicillin-susceptible *S. aureus*	22	9
Methicillin-resistant *S. aureus*	24	2
Coagulase-negative staphylococci	28	14
Enterococcus sp	7	3
Streptococcus agalactiae	5	5
Streptococcus pyogenes	1	1
Streptococcus bovis	–	2
Other streptococci	6	11
Aerococcus urinae	–	1
Clostridium perfringens	1	–
Corynebacterium spp	–	1
Propionibacterium acnes	–	1
Escherichia coli	4	6
Pseudomonas aeruginosa	4	1
Enterobacter cloacae	1	1
Proteus mirabilis	1	1
Pasteurella multocida	–	2
Acinetobacter spp	1	–
Serratia marcescens	–	1
Salmonella spp	–	1
Klebsiella pneumoniae	–	1
Morganella morganii	–	1
Bacteroides fragilis	–	1
Candida albicans[+]	1	–
Culture-negative infections	6	4

* Occurring after 2 years post-implantation
[+] Co-infection with *S. aureus*

Median and mean costs for the examinations performed were 450 and 675 CHF respectively (range 100–11 169 CHF). The median costs for these additional exams for the subgroup of late PJI was 910 CHF. Median hospitalisation costs were 39 964 CHF. On average, the exams cost 2% of the costs of the entire hospitalisation. In the summer of 2011, 1 US$ equalled 0.80 CHF.

Discussion

In contrast to a simple and cost-free medical history, "blind" additional radiological or clinical exams failed to reveal any clinical or financial benefit in the search for the origin of PJI. This finding was confirmed in all subgroups of analyses: Gram-positive infections, late PJI, and bacteraemic PJIs. The only case that developed a future hepatocellular cancer was preceded by a PJI due to *S. bovis*, an association that is already found in the literature [3].

Patient medical history was particularly productive in haematogenous Gram-negative PJI occurring late, i.e. after 2 years following prosthetic implantation, and were chiefy due to urinary sepsis or gastrointestinal infections that are not at all occult. The relative financial proportion of additional examinations performed was small (2%) compared to the overall hospitalisation and treatment, but in absolute terms they represented an average financial loss of 675.- CHF per PJI case, and this does not include other concomitant expenditures such as manpower and organisational resources. Our findings are consistent with the literature, thus excluding a major selection bias. Swan et al. [5] determined potential sentinel infective events occurring prior to knee PJI. Besides a high number of co-morbidities, they identified recent cellulitis as the only variable associated with future infection. All sentinel cases were visible externally and were well recalled by patients without the need for further investigation

Despite their worldwide occurrence, it is unclear whether patients with unusual pathogens or haematogenous PJI require investigation for underlying cancer or occult abscesses. Following extensive epidemiological research, *S. bovis* [3] and *Clostridium septicum* [6] remain the only sentinel pathogens that suggest an underlying neoplasm. Exclusion or confirmation of cancer with these pathogens at an early stage is likely to be cost-effective [3].

Similarly, there is probably no benefit from additional examinations regarding occult abscesses. Two reasons argue against this presumption. First, few severe remote infections will eventually seed to prosthetic joints [7]. Second, almost all remote infections are presumably eliminated during antibiotic therapy of 6 weeks or longer, which is standard for PJIs [2, 8]. It was not surprising that we failed to detect any residual remote infection following the end of treatment for PJI, except for the local arthroplasty infection itself [9]. To the best of our knowledge, the literature does not report any re-infection of a prosthetic joint from the same identified remote source as in the first episode. Rather, most PJI recurrences are due to incomplete surgical debridement, multi-resistant or small-colony variant pathogens, or suboptimal antibiotic therapy [2, 9].

A theoretical concern may be mentioned regarding occult endocarditis in the case of bactaeremic PJI, since the treatment plan for an infected total hip arthroplasty combined with an infected heart valve may not be the same as an isolated PJI. While the minimal durations of antibiotic therapy for PJI may exceed those for endocarditis, the recommended duration for initial intravenous administration is set at two weeks for a sole PJI [2], but is up to 6 weeks for endocarditis (depending on the pathogen) [10]. However, in reality, endocarditis is very often not occult but rather reveals other distinctive clinical features that a PJI usually does not have: underlying valvular pathology, intravenous drug abuse or catheterism, a high number of positive and sustained blood cultures, and peripheral embolisms together with a new heart murmur. In the absence of these hallmarks, a search for underlying occult endocarditis might not yield positive results. Indeed, in daily clinical life it is rather the contrary that is a problem. Endocarditis in arthroplasty carriers may occultly seed to the artificial joint. In our study all 3 cases of endocarditis were already known before the secondary PJI became symptomatic, and no additional echocardiographic exams revealed the presence of valvular vegetations in the absence of the above-mentioned hallmarks of endocarditis. We therefore think that the widespread habit of searching for occult endocarditis or spondylodiscitis in cases of *S. aureus* bacteraemia [10, 11] becomes of little value in established PJI in the absence of risk factors for endocarditis.

Our study has definite limitations, including the following. i) It is a retrospective, single-centre study with a large heterogeneity of the study population and of pathogens, thus limiting the possibility of generalising the findings; ii) Our conclusions are based upon epidemiological analyses and may not be regarded as a recommendation for every individual patient. iii) Some patients might have been followed up outside our institution. However, since most patients participated in the Geneva Arthroplasty Cohort Study [4, 7], and given the fact that Geneva University Hospitals are the only public (and the largest) hospital in the area,

Table 3: Cases of prosthetic joint infections (PJI) and neoplasms in the follow-up period.

Gender	Age	Immuno- suppression	Joint	Pathogen	Neoplasm	Diagnosis after PJI
Male	80 y	Dialysis	Hip	*Streptococcus agalactiae*	Epidermoid carcinoma of pharynx	1 year
Female	80 y	None	Hip	*Enterococcus*	Breast carcinoma	4 years
Male	56 y	Diabetes, alcoholism, cirrhosis	Knee	*Streptococcus bovis*	Hepatic carcinoma	4 years
Male	74 y	Dialysis	Hip	CoNS+	Epidermoid carcinoma	6 years
Male	81 y	None	Hip	MRSA°	Urothelial carcinoma	3 years
Male	72 y	Alcoholism, nicotine	Hip	*Enterococcus*	Pulmonary carcinoma	0.5 years

+ coagulase-negative *Staphylococcus*
° methicillin-resistant *S. aureus*

we consider this possibility very slight. iv) We witnessed a higher proportion of late-onset PJI in immune suppressed patients than has been reported in the literature. However, the explanation lies in the high number of haematogenous PJI or severely ill patients transferred to our university centre, whereas external primary surgical site infections are more likely to be treated by the surgeon who performed the arthroplasty. v) The short active follow-up time in 20% of our patients may be regarded as a limitation, since the current literature favours minimal follow-up durations of 1–2 years in osteoarticular infections. However, this concerns eventual recurrences of PJI. In contrast, the ideal follow-up time regarding the search for any underlying infection or cancer is unknown and may be rather short. In our study detection of the infectious origin occurred within 10 days and there were no surprises in further follow-up, with the exception of the case with hepatocellular carcinoma. vi) Our calculations used the most minimal attributed prices (excluding preparation costs, transport fees, contrast liquids etc.). Real costs may be higher.

If our findings are confirmed in larger studies, we feel it is safe to conclude that omitting blind additional exams in PJI is not deleterious. On the contrary, their avoidance helps to reduce costs and patient exposure to unnecessary examinations, invasive endoscopies or radiation. We emphasise that our opinion concerns the management of PJI and should not conflict with epidemiological prevention recommendations, such as general screening for colon cancer after the age of 50 [12] or colonoscopy for patients with risk factors for the disease [13].

Acknowledgments: We thank all colleagues of the Orthopaedic Service, Dr Philippe Garnerin for data retrieval and Abdessalam Cherkaoui from the Laboratory of Bacteriology.

Funding / potential competing interests: There is no financial support, grants, financial interests or consultancy that could lead to a conflict of interest. All authors state that they have read and approved the manuscript. It has not been published elsewhere nor is it under consideration for publication elsewhere.

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