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The multifactorial aetiology of fracture nonunion and the importance of searching for latent infection

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Objectives

A successful outcome following treatment of nonunion requires the correct identification of all of the underlying cause(s) and addressing them appropriately. The aim of this study was to assess the distribution and frequency of causative factors in a consecutive cohort of nonunion patients in order to optimise the management strategy for individual patients presenting with nonunion.

Methods

Causes of the nonunion were divided into four categories: mechanical; infection; dead bone with a gap; and host. Prospective and retrospective data of 100 consecutive patients who had undergone surgery for long bone fracture nonunion were analysed.

Results

A total of 31% of patients had a single attributable cause, 55% had two causes, 14% had three causes and 1% had all four. Of those (31%) with only a single attributable cause, half were due to a mechanical factor and a quarter had dead bone with a gap. Mechanical causation was found in 59% of all patients, dead bone and a gap was present in 47%, host factors in 43% and infection was a causative factor in 38% of patients.

In all, three of 58 patients (5%) thought to be aseptic and two of nine (22%) suspected of possible infection were found to be infected. A total of 100% of previously treated patients no longer considered to have ongoing infection, had multiple positive microbiology results.

Conclusion

Two thirds of patients had multiple contributing factors for their nonunion and 5% had entirely unexpected infection. This study highlights the importance of identifying all of the aetiological factors and routinely testing tissue for infection in treating nonunion. It raises key points regarding the inadequacy of a purely radiographic nonunion classification system and the variety of different definitions for atrophic nonunion in the current mainstream classifications used for nonunion.

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Article focus

- Are most fracture nonunions a result of a single identifiable cause, or of multiple causes?
- How frequently is indolent infection found in nonunions which are considered to be aseptic?
- How often are patient/host factors an issue?

Key messages

- A simple system for categorising the causes of nonunion into mechanical, dead bone/gap, infection and host factors can help the surgeon to treat all of the contributing factors.
- In order to maximise the chance of achieving successful bone healing at nonunion surgery, this study highlights the importance of looking for multiple causes and optimising systemic patient factors.
- Infection can only be confidently excluded by taking multiple appropriate tissue samples in every case of nonunion, as occult infection can present as a failure of healing, rather than with overt signs of infection.

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- Traditional methods of classifying nonunion by radiographic appearance can cause some confusion and need to be applied in conjunction with other assessments.

Strengths and limitations

- The distribution of causes is described for both nonunions with single and multiple aetiologies.
- The study is limited by the systematic bias associated with retrospective studies.

Introduction

Nonunion can be a devastating consequence of a fracture and the cause of a massive amount of patient morbidity. Nonunions also consume a vast amount of healthcare resources, with estimated costs of treatment ranging from £7000 to £79 000 per case.[1-4] Extrapolating from Scottish figures of 1000 cases of nonunion per annum,[5,6] the incidence of nonunion in the United Kingdom is around 11 700 cases per annum. This would suggest that nonunion costs the health services in the United Kingdom alone several hundreds of millions of pounds per year.

The optimal strategy for treating a disease is based on identifying its cause, and then removing or modifying this cause, in order to eliminate the disease. This methodology can be applied to patients who have developed a nonunion.

A range of factors have been recognised as contributing to poor bone healing and nonunion of fractures. These include patient systemic/host factors, infection, dead bone in association with a gap and an inappropriate mechanical environment.

Patient host factors, including comorbidities and medications, are known to impede the healing process. Data regarding host factors have been reviewed previously.[7] Infection in the presence of metalware can result in osteolysis, loosening and mechanical failure, with an even more detrimental outcome if the fracture is mechanically unstable.[8,9] An appropriate mechanical environment is crucial for bone healing.[9-11] Perren[12] indicates that the strain between the bone ends needs to be under 2% in order for the bone to bridge the fragments, and Yamaji et al[13] show that a 6 mm gap in sheep with either large or small amounts of micromotion adversely affects healing.

The local biology at the fracture site is important, with poor vascularity in the early stages associated with a small gap, and inadequate angiogenesis a key causative factor, particularly in atrophic nonunions.[14-16] Resultant dead bone from inadequate vascularity due to extensive soft-tissue stripping from either the initial injury, or subsequent operative interventions, has also been suggested to increase the risk of nonunion.

The various causes of nonunion can therefore be considered in the categories of infection, dead bone in association with a gap, an inappropriate mechanical environment and systemic/host factors. The aim of this study was to examine the frequency of these key causes in a large patient cohort at the time of the referral for nonunion.

Patients and Methods

A total of 100 consecutive patients who had undergone limb reconstruction surgery for the management of long bone nonunion, were reviewed. All patients were under the care of and the operation undertaken by two specialist consultant surgeons (GK and AHRWS) who provide a limb reconstruction service. The cohort included both patients treated for their fracture in the same hospital, and those that had been referred to the service from other regions. Patients under the age of 15 were excluded, as were patients with critical-size defects greater than 3 cm.

Information was obtained both prospectively and retrospectively from clinical visits and operation notes, radiographs and laboratory results. All patients had commenced treatment for nonunion at the start of the study. After analysis, the causes of the nonunion were identified and recorded. These causes were divided into four groups: mechanical; infection; dead bone with a gap at the nonunion site; and host factors. Any of these factors present in a case were recorded, thus the nonunion could be attributed to multiple causes. A senior consultant, senior trainee and junior trainee (AHRWS, GK, LM, JT, GH) considered each case and 'good agreement' was obtained between assessors.

An inappropriate mechanical environment was considered to be present if there was radiographic evidence of inadequate fixation/stabilistation of the fracture in its initial definitive primary management with subsequent excessive movement of fracture fragments and resulting excessive callus formation with or without occasional metalwork failure. The initial fixation was considered inadequate if it did not comply with standard (AO) principles, such as that used in plate fixation, six cortices either side of the fracture and with the intramedullary nail technique, the use of proximal and distal locking screws and an adequately fitting nail. It was also a contributing factor for some of the conservatively managed fractures (humeral and tibial) where there was excessive movement encountered at the fracture site.

Dead bone with a gap was recorded as a cause if the bone ends were atrophic on the radiograph and there was a non critical-size gap (greater than 4 mm). At operation, the bone was considered dead if it was not bleeding (i.e., the paprika sign was absent) and brittle when drilled or cut with an osteotome. Where possible, this was undertaken with a tourniquet so that bleeding from the soft tissues did not give a false impression of pinpoint bleeding on the bone surface.

Only host factors that were accepted risk factors for nonunion[7] were included. Smoking was considered a host factor if a habit of ten cigarettes or more per day was recorded. NSAIDs were only included as a host factor if

Table I. General patient data.

Age at time of injury (yrs)		**41.4 (16.7)**
Age at time of nonunion operation (yrs) (SD)		44.2 (16.3)
Gender % (male:female)		*74:26*
		Patients (n)
Bone	Tibia	53
	Femur	20
	Humerus	16
	Fibula	7
	Ulna	3
	Radius	1
Mechanism of injury	High energy:low energy (%)	*68:30*
	Open	34
Gustilo Classification (n)	I	6
	II	4
	IIIa	13
	IIIb	9
	IIIc	1
Pattern of injury	Simple:comminuted	41:57
Primary management	Conservative	14
	Intramedullary nail	34
	ORIF	34
	External fixator	17
Patients who had surgery for nonunion prior to referral		46
Operations for nonunion prior to referral (excluding the index procedure) (n)		
	0	54
	1	24
	2	11
	>2	12

SD, standard deviation; ORIF, open reduction and internal fixation

there was documented evidence of prolonged duration of use (i.e., more than 14 days). This was based on preclinical studies which demonstrated that impaired healing with NSAID treatment was time-dependent.[17-20]

In order to look for infection, multiple (at least three) samples were obtained for microbiology (each with different instruments). Samples were taken from the most abnormal-looking areas, primarily of soft tissues (as these are easier for the laboratory to process) and from the bone if it was surrounded by pus. Samples were also sent for histological examination to determine if there was an acute inflammatory response with neutrophils present using similar criteria as for revision arthroplasty surgery.[21] Whenever possible, antibiotics were stopped at least two weeks before the operation. However, if a patient became toxic or developed cellulitis, the antibiotics were restarted. This was necessary for four patients. At the time of this study, the samples were cultured for 14 days (this was extended to 19 days one year after the study). Infection was deemed to be present if, at the time of the nonunion operation, there were two or more positive deep tissue/fluid samples, or if there was frank infection under ongoing antibiotic suppression. Positive superficial wound and pin site swabs were not used to indicate that deep infection was present at the nonunion site.

A proforma was completed on each patient and the data were analysed with Microsoft Excel (Microsoft, Redmond, Washington) and SPSS (IBM, Chicago, Illinois).

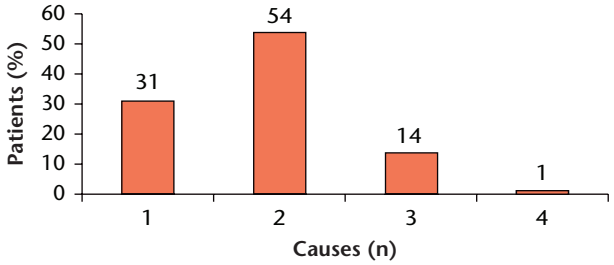

Fig. 1

Graph showing the number of causes per patient contributing to a nonunion.

Results

Patient data can be found in (Table I). The mean age of the patients at the time of the injury was 41.4 years of age (median 40 years, range 9.3 to 83.3, SD +/-16.5) and 44.2 years (median 42.3 years, range 15.4 to 83.9, SD +/-16.3) at the time of the index nonunion operation. The male:female ratio was 3:1.

Of the 100 nonunion patients, one was through an area of chronic osteomyelitis and one was in the dysplastic bone of a patient with neurofibromatosis. The remainder were related to trauma.

A total of 86 patients had nonunion, defined as having occured more than six months since the time of fracture, with no visible signs of progression to healing for three months. Ten patients had procedures earlier than six months (the earliest was at 16 weeks). In these patients there was a complete absence of any radiographic healing and no progression of healing in conjunction with either severe clinical infection or mechanical instability. The four remaining patients had well established 'mature' nonunions, but the specific date of their injury was not available.

The nonunions were predominantly in the lower limb (80 patients) and 38% were open injuries. Almost half of the nonunions (46 patients) had undergone further surgical intervention to treat the nonunion prior to referral.

Radiographs of the initial injury and nonunion had been destroyed for four patients, as had the clinical notes for one patient. Two further patients did not have the open/closed/ high energy nature of their fracture documented and histological data were not available for all of the patients.

Cause of nonunion. Only 31 patients had a single attributable cause. The remaining 69 had multiple identifiable causes of nonunion (Fig. 1).

Of those 31 patients, the breakdown was 48% mechanical; 16% infection; 26% dead bone and gap, and 10% host factors. Of the 69 patients with multiple factors, 54 had two causes, 14 had three causes and one patient had all four causes present (Tables II to IV).

Of the 43% who had a significant host factor, one third had more than one host factor and two thirds smoked more than ten cigarettes per day. A total of 42% of all

Table II. Combinations of causes in patients with one to four causes. Patients (n) with one* or two† causes.

	Mechanical	Infection	Dead bone/gap	Host
Mechanical	15*			
Infection	9†	5*		
Dead bone/gap	9†	9†	8*	
Host	15†	3†	9†	3*

Table III. Combinations of causes in patients with three or four causes. Patients (n) with three or four causes (presence indicated by •).

Patients (n)	Causes (n)	Mechanical	Infection	Dead bone/gap	Host
2	3	•	•	•	
4	3	•	•		•
3	3	•		•	•
5	3		•	•	•
1	4	•	•	•	•

Table IV. Frequency of different causes (%) found in 100 nonunion patients.

Attributable cause	Mechanical	Infection	Dead bone/gap	Host
Cases (%)	*58*	*38*	*46*	*43*

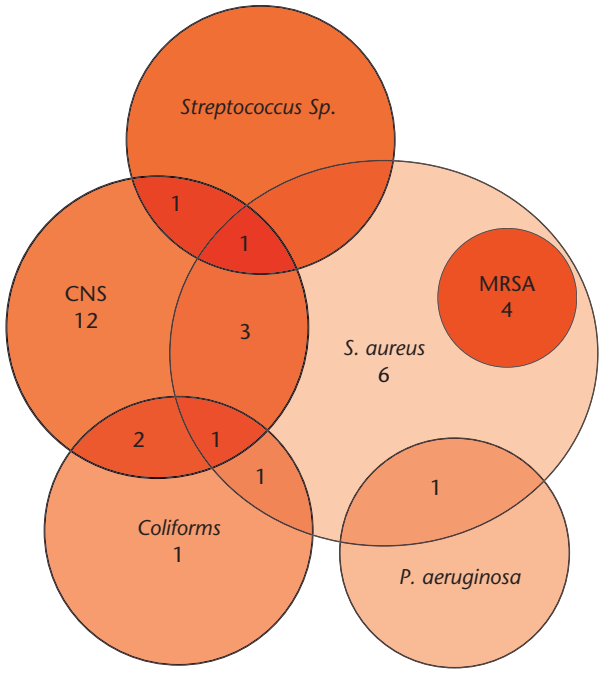

Fig. 2

Venn diagram showing the bacteria grown from intra-operative samples (n = 1 patient).

Table V. Intra-operative microbiology results compared with clinical suspicion of infection.

	Microbiology sample results			
Clinical diagnosis of infection at time of referral	No microbiology result found	Negative	Single positive result	Multiple positive results
No suspicion (n = 58)	1*	54	1 (spurious)	2*
Suspicion (n = 9)	0	7	0	2*
Previous infection (n = 8)	0	0	0	8*
Ongoing infection (n = 25)	0	5*	1*	19*

*Deep infection

patients admitted to smoking to some degree, and this counted as a risk factor in 27%. In all, nine patients neither smoked nor took NSAIDs, but had other host factors that were considered to contribute to the nonunion. These included excessive consumption of alcohol with secondary medical complications, poorly controlled diabetes, neurofibromatosis and inflammatory arthritis.

Infection. In all, 97% of patients had more than three samples sent. Table V compares the microbiological results from intra-operative tissue and fluid samples with the pre-operative clinical suspicion of infection.

A total of three of the 58 patients with no clinical suspicion of infection at the time of referral were found to either have multiple positive samples of coagulase negative *staphylococcus* (CNS, two patients) or a large abscess around the metalwork (microbiology result not available). All the patients had a white cell count/C-reactive protein (CRP)/Erythrocyte sedimentation rate (ESR) less than 10 (normal range CRP 0 mg/L to 10 mg/L, WCC 4.5 to 11x10^9/L, ESR< 15 mm/hr).

All of the eight patients who had been treated previously for infection but without any active ongoing infection, and who were considered to be free of infection, had multiple positive cultures. All of their available blood and serum markers were normal: white cell count (eight patients), CRP (seven patients) and ESR (six patients).

A total of 25 patients had ongoing clinically apparent infection: 19 had multiple positive cultures; one had a single positive result and a long-standing history of chronic osteomyelitis, and five patients had negative cultures but were on antibiotics at the time of surgery.

A Venn diagram (Fig. 2) illustrates the microbiological results of the patients with infection: ten had polymicrobial results and 22 grew a single species only. CNS was the most frequently grown bacteria, found in 56% of cases and the only isolated bacteria in 34% of all cases. *Staphylococcus aureus* was grown in 41%, with a further 12% (four cases) of methicillin-resistant *Staphylococcus aureus*. Coliforms were isolated in 16% of cases and were usually in association with a *staphylococcus* bacterium.

Table VI. Viable/vascular nonunion types of definitions compared.

Classification (viable/vascularised)	Weber & Čech[33]	AO[30]
A	Hypertrophic elephant foot; callus present, insufficient stability	Hypertrophic elephant foot; some stability and callus
B	Moderate horse hoof; callus present, 'somewhat' unstable	Hypertrophic horse hoof; less stability, fewer calluses
C	Oligotrophic with absent callus; rounded-off bone ends due to inadequate fracture reduction	Atrophic; unstable with consequent absorption and rounded-off bone ends

Table VII. Non-viable/ avascular nonunion types of definitions compared.

Classification (nonviable, avascular)	Weber & Čech[33]	AO[30]
Fracture type	Severe comminution with intermediate avascular fragments and necrotic bone edges	Comminuted fracture with intermediate fragments
A	Torsion wedge	Devitalised (immediately post trauma)
B	Comminution	Intermediate fragments healed but nonunion remains (mths later)
C	Defect (critical-size defect)	Nonunion persists after several yrs
D	Atrophic; as a result of residual gap with nonviable scar lacking osteogenic potential (as a result of bone loss from infection/ injury)	

Table VIII. Previous studies of long bone nonunion types.

Author	Bone	Atrophic nonunion	Oligotrophic nonunion	Hypertrophic nonunion
Megas et al[37]	Femur	25		5
Shroeder et al[38]	Femur	10		32
Zelle et al[39]	Tibia	21		19
Kloen et al[40]	Forearm	4	34	13
Babhulkar et al[22]	Long bones	52		61
Flierl et al[34]	Long bones	30	41 (described as normotrophic)	12
Current study	Long bones	81		15

Discussion

A total of 100 consecutive patients treated for long bone nonunion were analysed. The majority of patients were young men (mean age 44) with tibial fractures and who had been primarily treated with operative fixation. This is in keeping with several previous studies of nonunion.[22-25] It has been reported that high-energy and open injuries can predispose patients to healing problems due to the extent of the soft-tissue injury;[24,26-28] 34% of the nonunions have been shown to follow open fractures, which constitutes only 2.6% of all fractures,[29] suggesting that the open nature of the fracture increases the rate of nonunion by a factor of 19.

Nonunion has been classified several times.[30-33] Most surgeons employ either the Weber and Čech[33] or AO classification.[30] Both classifications suggest nonunions have viable and nonviable types; those in the viable group are considered to have the biological ability to heal but are prevented by underlying mechanical/instability issues, whereas the nonviable group consists of comminuted devascularised fractures that do not have the blood supply to heal. These classifications divide patients on the basis of their radiological appearance and are used to infer the biological viability at the nonunion site (Tables VI and VII). With hypertrophic nonunions the radiograph may be a reasonable indicator of the biology (vascular and active), however, the atrophic nonunions can have a similar appearance on the radiograph to the oligotrophic group, yet their biology is very different. The classification of their subtype based on radiographs alone is very subjective and challenging.

Several terms have been used by surgeons to describe the radiographic characteristics of types of nonunion (atrophic, oligotrophic, hypertrophic, pseudarthrosis, fibrous, mobile and normotrophic),[34] often with different interpretations, in particular regarding atrophic nonunion and pseudarthrosis.

The nonunion subtype recognised to be vascular/viable but lacking callus and with rounded off bone ends is 'atrophic' according to AO,[30] but 'oligotrophic' according to Weber and Čech.[33,35] The Weber and Čech atrophic nonunion is very different: avascular and nonviable as a consequence of a severely comminuted fracture "developing after a prolonged period of time (years) having a gap of bone loss (from comminution) and filled with non-viable scar and thus avascular as a consequence". The AO classification does not recognise the existence of oligotrophic nonunion in its classification system.

Confusion aside, these classifications are primarily radiological and they do not take into account infection

or host factors. Recently, there has been an attempt to address this with a new classification system – the nonunion scoring system, which incorporates patient factors into its scoring system.[31,36]

There are few series reporting on all types of long bone nonunion in a single patient cohort (most nonunion studies concentrate on a single anatomical site, such as the scaphoid). These studies are tabulated in Table VIII[22,34,37-40] which compares previous publications and illustrates that there is no clear pattern of common distribution between the types of nonunion using this classification. This may reflect a different case mix or a difference in the classifications used (AO *versus* Weber and Čech).

Mechanical and dead bone were the most frequently occurring causes in our study, at 59% and 47% respectively, with infection being a cause in 38% and host factors in 43% of cases.

The ideal mechanical environment is dependent on the technique of fracture healing applied (direct *versus* indirect) and on the time point after the injury. The technique of fracture repair (direct *versus* indirect) used in the initial procedure was taken into account when assessing whether the mechanical environment would have been satisfactory or suboptimal. By assessing the initial post-operative radiographs, we were able to clarify that inadequate mechanical fixation was a problem at the outset, rather than a result of the nonunion. With direct healing, rigid fixation is required throughout. For indirect healing, a degree of axial micromovement is beneficial, provided it is not excessive.[10,13,41] In clinical practice, transverse shear movement is associated with nonunion, however, shear movement at 45° in an animal model did not inhibit healing.[42] The mechanical causes included inadequate external fixation constructs with a long distance from diaphyseal half pins to the metaphyseal fixation, resulting in a large amount of shear at the fracture site; inappropriate choice of plate (i.e., too thin or short an implant); severely inadequate reduction, and absent locking of intramedullary nails. As mechanical error was the most significant contributing cause, it is essential not only to try and prevent this occurring in the first instance, but also to ensure that it is recognised and dealt with definitively when treating the nonunion.

Several studies have shown that even a small defect can delay healing or increase the risk of nonunion.[43-45] A recent paper from a multicentre randomised controlled trial showed a significant increase in the risk of re-operation with a gap of even a few millimetres after tibial nailing.[45]

Almost half of our patients had a significant host factor. This concurs with the findings of Niikura et al[46] and indicates the importance of searching for a medical factor which can be corrected. Smoking has been associated with nonunion,[47-50] however, the critical level at which smoking becomes a significant risk is difficult to determine. We attributed smoking as a risk factor if there was evidence of a habit of more than ten cigarettes per day (28 patients). This number has been used in other studies as an acceptable cutoff point[49,51] and patients are thought to under (rather than over) estimate their daily habit. Nonetheless, there are no clear data to validate ten per day as the critical number, and we therefore recorded the extent of the smoking habit in all patients. The data on non-steroidal anti-inflammatory drugs are variable, with a considerable deficiency of high-quality evidence available in the literature, but overall preclinical data suggest that COX-2 selective agents are particularly deleterious for fracture healing. A short course of non-steroidals (i.e. one week) delays healing, but a prolonged treatment results in nonunion.[17,20,52] Clinically, this is supported by a 282-patient review of the prevention of heterotopic ossification around acetabular fractures, which reported a significantly higher rate of nonunion in peripheral fractures in the patients on indomethacin.[53] A recent retrospective clinical study of 1900 patients with a fracture of the long bone suggests that post-operative NSAIDs double the risk of healing complications.[54] In the current series, these agents were only considered to have a contributing effect if there was a history of prolonged use of aspirin or NSAIDs.

As some patients were tertiary referrals, data on the condition of the soft tissues and the timing of flap cover of open fractures, which have been implicated in nonunion, were not available. However, in established nonunions, these factors would mainly contribute by increasing the risk for infection, for which the patients were diligently examined.

Infection made up a significant part of the cohort (38%) and was the single cause of the nonunion in 7% of cases. The most common bacteria cultured were staphylococci (94%). Other studies have found similar results, yet in contrast to our series previous papers more frequently cultured *Staphylococcus aureus* than *Staphylococcus epidermidis*, with lesser numbers of enterococci, *pseudomonas* and *Klebsiella*.[37,55-57]

Of the 58 patients with closed injuries, no suspicion of infection and who were thought to have aseptic nonunions, three turned out to be infected (5.2%) and two of nine patients (22%) with no infective history, but with clinical suspicion of infection, were also positive. It is accepted that infected arthroplasty patients usually present with signs of loosening rather than signs of infection.[58,59] We consider that it is important to recognise that, in an analogous way, fracture patients with occult infection may present with a failure of healing rather than systemic signs of infection. It is therefore prudent to consider that every nonunion patient has infection until proven otherwise, as failure to recognise and treat the latent infection may result in unsuccessful treatment of the nonunion.

Over two thirds of patients in this cohort had more than one cause for their nonunion. Although alluded to anecdotally, a PubMed search for nonunion/nonunion AND cause/aetiology did not reveal any studies that had quantified the relative frequency of the causes or carried out a similar analysis of the patterns of causes as undertaken in this study.

Half of the patients had undergone previous unsuccessful surgery for nonunion elsewhere. This may suggest a more complex cohort than that encountered in general orthopaedic practice and that a single, rather than multiple, causes had been considered at the time of the initial revision surgery.

In conclusion, multiple causes contributing to nonunion were found in 69% of patients. This highlights the importance not to assume a single cause when managing a case of nonunion. Currently, the most commonly used classification systems for nonunion are based upon radiographic changes and do not take other influential factors into account.

Infection was found entirely unexpectedly in 5% of patients. Multiple tissue samples should be taken at all nonunion surgery to exclude occult infection. The Weber and Čech classification has subtle but fundamental differences, compared with the AO classification (particularly 'atrophic' in the discussion of vascularity), potentially causing misunderstanding between those who use these classifications, both in clinical and research circumstances.

Supplementary material

A table showing the number of patients who smoked and frequency are available online alongside this article at www.bjr.boneandjoint.org.uk

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Author Contribution

- L. Mills: Study design, Data collection, Data analysis, Manuscript preparation.
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- G. Hopper: Data collection, Data analysis.
- G. Keenan: Data collection, Data analysis.
- A. H. R. W. Simpson: Study design, Data analysis, Manuscript preparation.

ICMJE conflict of interest

- None declared