

Bone flap infections after craniotomy. a review of 63 cases and the implications for definitions, classification and surveillance methodologies

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CITATION

O'Donnell, Sinead; Creedon, M; Walsh, J; Dinesh, Binu; O'Brien, D P; MacNally, S; et al. (2023): Bone flap infections after craniotomy. a review of 63 cases and the implications for definitions, classification and surveillance methodologies. Royal College of Surgeons in Ireland. Journal contribution.
<https://hdl.handle.net/10779/rcsi.22495663.v1>

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Manuscript Title

Bone flap infections after craniotomy. A review of 63 cases and the implications for definitions, classification and surveillance methodologies.

Manuscript Category

Original Articles

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Running Title: Bone flap infections. A review of 63 cases

Key words: Bone flap infections; craniotomy; craniectomy; *Staphylococcus aureus*; surgical site infection

Word Count = 2,100

SUMMARY

Background: Bone flap infections (BFI) occur following neurosurgical procedures such as craniotomies. However, they are poorly defined and often not clearly differentiated from other surgical site infection neurosurgery.

Aim: To review data from a national adult neurosurgical centre to explore some clinical aspects to better inform definitions, classification and surveillance methodologies.

Methods: We retrospectively reviewed data on clinical samples sent for culture from patients with suspected BFI. We also accessed information recorded prospectively from national and local databases for evidence of BFI or related conditions based upon terms used in surgical operative notes or discharge summaries and documented monomicrobial and polymicrobial infections related to craniotomy sites.

Findings: Between January 2016 and December 2020, we documented 63 patients with a mean age of 45 years (16-80). Craniectomy for infection of the skull was the most common terminology used to describe BFI in the coding used in a national database, 40/63 (63%), but other terms were used. A malignant neoplasm was the most common underlying condition necessitating craniectomy in 28/63 (44%) cases. Specimens submitted for microbiological investigation included 48/63 (76%) bone flaps, 38/63 (60%) fluid/pus, and 29/63 (46%) tissue. Fifty-eight (92%) patients had at least one culture positive specimen; 32 (55%) were monomicrobial and 26 (45%) were polymicrobial. Gram-positive bacteria predominated and *Staphylococcus aureus* was the most common.

Conclusion: Greater clarity on how to define BFI is required to enable better classification and the carrying out of appropriate surveillance. This will inform preventative strategies and more effective patient management.

Abstract word count = 247 (limit=250).

Introduction

Healthcare-associated infections (HCAI) in neurosurgical units represent a clinically significant burden. In a Polish study, the overall prevalence of HCAI was 1.4% or 2.7 per 1,000 patient days but in neurosurgery, the rates were 2.8% and 5.2/ 1000 patient days [1]. Furthermore, antimicrobial treatment can be complicated where multi- drug resistance (MDR) is prevalent. In a Spanish study, 6.52% of neurosurgical patients carried extended spectrum-beta lactamase producing Enterobacterales [2]. This would preclude the use of third generation cephalosporins, commonly used in meningitis and other neurosurgical infections.

Surgical site infections (SSI) in neurosurgical patients are especially important. In a recent UK review, the prevalence of SSI in general surgery was 1.4% compared with 4.3% in neurosurgery [3]. This is similar to North American and European data [4-7].

Superficial SSI may occur after a craniotomy (i.e. opening the skull) or craniectomy (i.e. removal of part of the skull such as to control raised intra-cranial pressure). Bone flaps are created during craniotomy or craniectomy procedures. Post craniotomy, the bone flap is usually replaced and fixed to the adjacent calvarium during the procedure. In a decompressive craniectomy (DC), the skull is opened and a bone flap is removed to assist in controlling raised intra-cranial pressure (ICP). The bone is cryopreserved or preserved in a pocket in the abdominal wall [8-10], and may be replaced back into the skull at a later date as an autogenous cranioplasty (i.e. repair of skull bone defect).

In a recent systematic review of 59 studies, complications arose in a quarter of cases after cranioplasty and 10% of these were infections [9]. Management of bone flap infections usually requires prolonged antimicrobial treatment, removal of the bone flap and delayed allograft

81 cranioplasty. This is associated with the loss of skull integrity and brain protection, significant
82 cosmetic deformity, and further re-operations if secondary cranioplasty is undertaken [11].

83
84 When assessing the prevalence and risk for developing BFI, one needs to consider the
85 indications for the original surgery, if the bone flap was removed, how it was stored, and the
86 underlying disease of the patient. Furthermore, sometimes a bone flap prosthesis may be used
87 during cranioplasty, composed of polyetheretherketone (PEEK). As this represents a foreign
88 body, if infected, it may present additional challenges in treatment. The risk factors for BFI
89 after multi-variate analysis include an American Society of Anesthesiologists score of greater
90 than two and re-intervention after the first craniotomy [7]. The microbiological causes of BFI
91 are varied; in a Spanish study, the most common causative organisms were Gram-positive, i.e.
92 *Cutibacterium acnes* (23%) and *Staphylococcus epidermidis* (23%) with *Enterobacter cloacae*
93 accounting for approximately 1 in 8 infections [7].

94
95 We retrospectively reviewed patients with suspected BFI from a national adult neurosurgical
96 centre to explore some clinical aspects and characteristics, to better inform definitions,
97 classification and surveillance methodologies.

Methods

Setting

Beaumont Hospital is an 800-bed largely adult tertiary referral centre, which contains the Irish national centre for neurosurgery, including a 10-bed dedicated neurosurgical intensive care unit, three dedicated neurosurgical theatres plus another emergency theatre. Each year, approximately 2,400 neurosurgical procedures are performed, including approximately 550 craniotomies. There is a close continuous clinical relationship between the departments of neurosurgery and clinical microbiology regarding diagnostic approaches, treatment of suspected or confirmed infection, infection prevention and control, and antibiotic stewardship, including multi-disciplinary rounds [12, 13].

Data Sources

Patients with suspected BFI between January 2016 and December 2020 were retrospectively evaluated (Figure 1). In the absence of international agreement, our working definition was infection at the surgical site in any patient after a craniotomy where any data or documentation suggested or indicated a diagnosis of BFI. An analysis was performed on data collected and recorded prospectively from a variety of sources.

We identified all patients who underwent a craniotomy in Beaumont Hospital (July 2015 – December 2020) and might subsequently have developed a BFI from January 2016 via electronic operating theatre records. This dataset was then cross-referenced with the hospital in-patient enquiry (HIPE) database. The HIPE database is used in Ireland to monitor and collect data on acute hospital admissions to assist in planning service provision. The HIPE database coders assign diagnosis and procedure codes to patients on discharge from hospital. Patients admitted under a neurosurgical team with HIPE diagnosis coding suggestive of a possible BFI

(wound infection following a procedure, bone graft failure/rejection, failed/rejected transplant) were further analysed. The dataset was further refined through a review of digital operative notes, discharge summaries and the microbiology laboratory database for each patient to identify features suggestive of possible BFI (e.g. reference to BFI made in operative notes or discharge summaries or bone flap specimens submitted for culture) and the microbial aetiology.

The study was reviewed and approved by the Beaumont Hospital Clinical Governance and Audit Department.

Results

In total, there were 3042 craniotomies. (Jul-Dec 2015 = 272, 2016 = 550, 2017 = 605, 2018 = 530, 2019 = 573, 2020 = 512). Sixty-three patients were identified with possible BFI (female: 28; male: 35) with a mean age at the time of surgery of 45 years (range: 16 -80). The neurosurgical characteristics of these 63 patients, including how many needed to have more than one craniotomies as well as the sources of data are outlined in Table. Indications for the original craniotomy included; malignant neoplasm (28), benign neoplasm (12), haematoma (9), epilepsy (4), aneurysm (3), cerebral infarction (2), infection (abscess) (2), trauma (2) and haemangioma (1). A BFI was documented in 26/58 (45%) discharge summaries while removal of a bone flap was documented in 25.

All 63 patients had intra-operative specimens submitted to the clinical microbiology laboratory. Two hundred and one specimens were received with an average of four specimens submitted per patient (range 1-11). An analysis of these intraoperative specimens revealed that in 48/63 (76%) a bone flap, 38/63 (60%) fluid/pus, 29/63 (46%) tissue and a further 51/63 (81%) patients had swab specimens submitted to the microbiology laboratory. Fifty-eight of 63 (92%) patients had at least one culture positive specimen; 32 (55%) were monomicrobial and 26 (45%) were polymicrobial. The organisms isolated are outlined in Table 2. *Staphylococcus aureus* was the predominant organism isolated (39/58; 67%) and predominated in monomicrobial culture (21/39; 54%). When isolated in a polymicrobial culture, *S. aureus* was most commonly isolated with *Cutibacterium/Propionibacterium* species (11/15; 73%). In polymicrobial infections, the majority had two organisms isolated (21/26, 81%). Anaerobes were isolated in five patients. Only one patient was documented as having had a PEEK bone flap inserted, from which two *Candida* isolates were recovered, both of which were fully susceptible to fluconazole, amphotericin B and echinocandins.

Discussion

This study was prompted by our wish to better understand how common these infections are in our patient cohort and to explore exactly what this term means in the absence of an agreed definition, as BFI and organ space infection are not synonymous. With a national neurosurgical unit in our hospital and in the absence of national surveillance of post-operative infections, we have documented our experience using a working definition to prompt interest elsewhere in this condition. Using a national database, i.e. HIPE, internal operating theatre notes, laboratory and discharge data, we retrospectively identified 63 patients over five years. However, given the various terms used, some of which suggested but were not confirmed as BFI, we may have underestimated or overestimated the true number occurring over the five years. Nonetheless, the data is of some clinical significance given the daily liaison there is between the neurosurgical and clinical microbiology teams.

The most common microbial aetiology was *S. aureus*, as described elsewhere [14] with Gram-positive bacteria being more common than Gram-negative bacteria. Multidrug resistant organisms including MRSA, extended-spectrum beta-lactamase (ESBL) producing Enterobacterales and inherent AmpC producing Enterobacterales such as *Enterobacter cloacae* and *Serratia marcescens* accounted for some infections, but no carbapenemase-producing Enterobacterales were isolated. Anaerobes were isolated in five cases. The empiric treatment regimen used in our institution for BFIs and extra-dural surgical site infection is vancomycin, ceftriaxone and metronidazole, and with rapid escalation during on-going clinical liaison such as when an ESBL producing Enterobacterales is identified. We found there was a wide variation in the number of specimens obtained for culture, from one to 11 specimens per patient, highlighting the need for a protocol in the diagnosis of BFIs.

Surgical site infections are an important complication of neurosurgical procedures and range from superficial to deep [4-7]. Bone flap infections do not appear to neatly fit in to the classification of SSI as either superficial or organ space. In a nested case-control study of SSI after craniotomy and craniectomy only 11.5% had superficial infection but 52% had organ space infection with meningitis, the most common pathogen was *S. aureus* either alone or in combination, and compared to controls, patients with SSI were more likely to require re-admission with a longer length of hospital stay [14]. The authors in the same study identified Gliadel wafer use and a post-operative CSF leak as procedure-related risk factors. Hence, unlike with other categories of surgical procedures, the proportion of SSI that are deep-seated or organ-space are relatively high with implications for outcome and hospital costs. Some of what is described as deep or organ-space infection may represent BFI.

While cranioplasty is a relatively common procedure, especially to treat traumatic brain injury (TBI), it is associated with complications. In 40 of 59 studies in a meta-analysis, infection complications were recorded with a rate of 10% overall but were slightly higher in those with TBI; the overall complication rate (including seizures, haemorrhage etc.) was 24.6% [8]. When DC is required to control ICP, the removed bone may be stored subcutaneously in fat layers of the abdominal wall of the patient or be removed completely from the patient and stored by cryopreservation, i.e. in a freezer at -70°C. In a randomised clinical trial comparing both methods of bone storage in 143 patients after DC, the overall BFI rate was 4%, and was statistically associated with older age; all four infections were in the cryopreservation group, where the rate was 8%, and all were caused by methicillin-resistant *S. aureus* (MRSA) [15]. While the infection rate appears to be lower with subcutaneous storage and this approach obviates the need for storage facilities for removed bone, trying to preserve living tissue before

it is re-used later has its challenges, and there is a risk of bone flap resorption [15]. Pre-implantation bacteriological cultures from cryopreserved bone flaps have been suggested by some as a measure to prevent BFIs [16]. However, one retrospective study did not find an association between re-implantation of bone flaps with positive cultures and subsequent SSI but found that operative skin preparation including allowing the skin to dry adequately post antisepsis reduced the risk of SSI [17].

Despite the limitations in our study, namely it being single-centered, the relatively small number of patients reviewed, the absence of controls, the possible misclassification on the HIPE database, and the variable terms we used to identify cases, our findings highlight some key issues. These include the absence of an agreed definition of BFI, how to confirm the diagnosis and categorise, the need to agree appropriate surveillance systems and the optimum specimens to determine a microbial aetiology.

Conclusions

We retrospectively reviewed prospectively collected data on what we considered BFI, based on a working definition, in the absence of agreement on what constitutes this condition. While we have documented some aspects such as possible risk factors and microbial aetiology, it is clear from the scientific literature that this condition is poorly characterised and understood. There is a need for a consensus definition, criteria for diagnosis, classification and ongoing appropriate surveillance that might help us better understand BFI. Appropriate surveillance should be multi-centre and multi-disciplinary, prospective, and involve the collection of data on risk factors, treatment regimens and outcome, after an agreed minimum period of follow-up. Addressing these will better inform our comprehension of the epidemiology of BFI, provide

239 a focus for specific preventative measures, and possibly improve the management of this
240 condition.

241 Word Count = 1,986

242

243 **Figure 1.** Search strategy for identifying patients with suspected bone flap infection (BFI).
244 (HIPE, hospital in-patient enquiry)

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250 **Acknowledgements**

251 The authors are grateful for the contribution of nursing, audit, clerical, scientific and
252 administrative staff of the departments of clinical microbiology and neurosurgery in the
253 diagnosis and management of these complex patients.

254

255 **Conflict of Interest Statement**

256 All other authors declare that they have no conflict of interest related to the contents of this
257 manuscript.

258

259 **Funding**

260 There was no external or internal funding to support this project.

261

262 **Authorship**

263 HH conceived the project and led in the drafting of the manuscript. SOD, MC and JW
264 collected the data with SOD analysing and collating the data. All authors reviewed draft
265 manuscripts and approved the final draft.

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