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FOCUS SESSION

Management and prevention of cranioplasty infections

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Abstract

Background Infection may complicate the outcome of cranial repair with significant additional morbidity, related to hospitalization, surgery and long antibiotic therapy, that may become even dramatic in case of multi-resistant germs and in particular in the paediatric population. Additionally, the economic costs for the health system are obvious. Moreover, surgical decisions concerning the timing of cranioplasty and choice of the material may be strongly affected by the risk of infection. Despite, management and prevention of cranioplasty infections are not systematically treated through the literature so far.

Methods We reviewed pertinent literature dealing with cranioplasty infection starting from the diagnosis to treatment options, namely conservative versus surgical ones. Our institutional bundle, specific to the paediatric population, is also presented. This approach aims to significantly reduce the risk of infection in first-line cranioplasty and redo cranioplasty after previous infection.

Conclusions A thorough knowledge and understanding of risk factors may lead to surgical strategies and bundles, aiming to reduce infectious complications of cranioplasty. Finally, innovation in materials used for cranial repair should also aim to enhance the antimicrobial properties of these inert materials.

Keywords Bundle · Cranial repair · Cranioplasty · Infection · Pediatric head injury · Prevention · Personalized medicine

Introduction

Cranioplasty may be burdened by significant morbidity, with rate of major complications between 10.9 and 40.4% and infectious ones ranging from 5 to 33% [9, 10, 12, 16, 32, 37]. Some risk factors for infection of cranioplasty are analyzed through the literature. However, the impact of other factors, such as skin contamination by multi-resistant germs in long-hospitalization patients, on the strategy and outcome of cranial repair is neglected so far. This may, instead, also affect the timing of cranioplasty.

Furthermore, the management of cranioplasty infection is somehow borrowed from the experience with other prosthesis and is not standardized. Examples of this come from the lack of consensus on the management of cranioplasty infection, with removal versus retention of the prosthesis, and the timing of redo cranioplasty after previous infection.

The present paper focuses on infection of cranioplasty, in particular prevention and management options. The pertinent literature is reviewed, and an institutional bundle is presented.

Infection of cranioplasty

Infections may be classified according to their localization into superficial, bone flap osteitis, epidural infection and organ one [10]. Incidence widely varies in the literature ranging from 5 up to 33% [5, 9, 10, 12, 16, 20, 32, 37]. Time of presentation ranges from a few days to some months from surgery. Accordingly, infections may be classified as early or late, if occurs before or after 4 weeks from the cranioplasty implantation, respectively [15]. The most common symptoms

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are fever, local signs of inflammation (swelling and/or redness at the operated site), wound drainage and/or dehiscence, wound pain/headaches, seizures and focal neurological deficits [5]. The diagnosis is completed by laboratory tests (white blood count and C-reactive protein, CRP) and radiological exams (contrast-enhanced CT scan and MRI scan), showing contrast-enhancing lesions (Fig. 1). As this finding could be unspecific, some authors suggest the superiority of the MRI scan on the CT scan due to the possibility to use diffusion-weighted images (DWI) that consent to clearly identify purulent material and bone involvement, thus allowing differential diagnosis with scarring tissue [43]. The pathogenesis of the flap infection is most likely due to microbial contamination at the time of surgery, especially in trauma setting and in cases of bifrontal craniectomy. In the first case, the dynamic of the trauma and the frequent presence of superficial wound may favour the access to bacteria of the skin and to the ones present onto the impact surface [38]. Furthermore, fractures involving the paranasal sinuses or the mastoid air cells can create a communication between the intracranial space and the outer one. Similarly, the need for bifrontal craniotomy increases the risk of infection due to the eventual violation of the frontal sinus [17, 48]. On these grounds, the most common pathogens are those of the skin and of the paranasal cavity such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Propionibacterium acnes*, followed by anaerobic bacteria of the nasal cavity [5, 12].

The pattern of pathogens may reflect differences in the causing factors associated respectively to early and late infections. In fact, early infections are supposed to result from skin flora bacteria introduced at the time of surgery whilst late infections are unlikely connected with the surgery itself. The latter may result from the hematogenous diffusion of bacteria, which either stay dormant for months or diffuse from other site of infection. Rosseto et al., in fact, report the existence of a systemic infection as one of the risk factors for cranioplasty infection [40]. Similarly, Rocque et al. consider the existence of devices, such as tracheostomy or gastrostomy, that are usually related to severe head injury and poor neurological status, a risk factor for cranioplasty infection [39]. These patients peculiarly stay longtime in the hospital, and in particular in the intensive care unit, and we may easily suppose that this results in skin contamination by multi-resistant bacteria.

Finally, as for other neurosurgical and non-neurosurgical devices, the possibility of colonization from transient bacteremia may represent a crucial factor in the development of a late infection. In fact, the occurrence of transient and spontaneous *S. epidermidis* bacteremia in patients and in healthy humans has been proven since longtime [52].

The impact of these infections is extremely high, since they usually complicate a long clinical history with additional morbidity, related to hospitalization, surgery and long antibiotic therapy. Finally, the costs for the health system are easily understood.

Management of cranioplasty infections

Literature focusing on the management of cranioplasty-associated infections is scant, and there is no agreement on how to treat it. For alloplastic materials, some general concepts may be borrowed by the literature dealing with other prosthesis. On the other hand, autologous bone cranioplasty has specific features that should be evaluated.

Prompt diagnosis of infection of the cranioplasty is the first step [5] to choose the adequate management. Evidence of infections are immediate when clinical presentation is acute with fever and local signs of inflammation (erythema, local warmth or wound drainage), whilst late infections might be silent or present with more subtle symptoms [15]. In general, management options of infection of cranioplasty vary from conservative ones with retention of the cranioplasty to more aggressive one based on its removal along with long antibiotic therapy.

Regardless of the chosen approach, when bone flap–associated infections are suspected, prior to germ

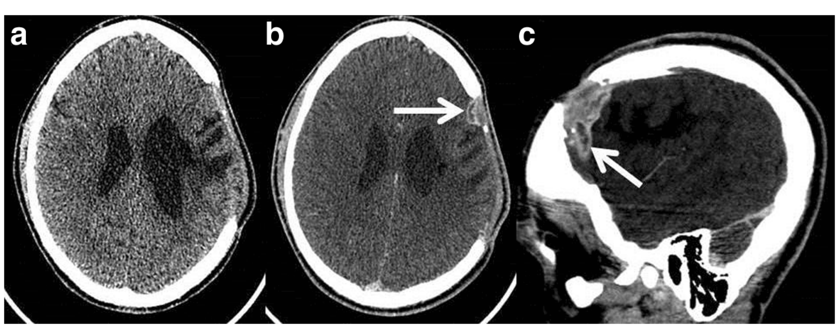

Fig. 1 Left cranial decompression for head injury, followed by autologous cranioplasty complicated by infection by *Pseudomonas aeruginosa*, treated with removal of the bone flap and 6-week antibiotic therapy. Three months after resolution of the infection, CT scan without contrast administration acquired for manufacturing the customized prosthesis ruling out any residual collection (**a**). After contrast medium administration, a focally enhancing lesion was evident under the frontal portion of the skin flap (**b** and **c**, arrows). Since the patient did not show any signs of infection, surgical toilette was performed along with microbiological samplings before planning cranioplasty

identification, empiric antimicrobial treatment covering Gram-positive and Gram-negative germs has to be started. Thereafter, conservative or aggressive treatment is chosen depending on the identified bacteria. In both types of strategy, the appropriate response to therapy must be ascertained and followed over time, monitoring systemic and local clinical signs and biochemical markers, although the last ones may show low specificity [5, 19].

Concerning conservative treatment, some authors proposed a wash-in wash-out indwelling antibiotic irrigation system associated with scrubbing of the bone flaps with povidone-iodine solution and soaking in 1.5% hydrogen peroxide, associated with wound debridement [3].

Conservative treatment has been proposed not only for autologous bone flaps but also in some cases of infected alloplastic cranioplasty. Biomimetic materials claim the opportunity to manage conservatively the infection with antibiotic therapy. Iaccarino et al. presented four cases of severe septic complication following cranioplasty with porous hydroxyapatite (HA) conservatively treated without flap removal [23]. The authors assert that such a result has been obtained thanks to the combination of a targeted antibiotic therapy, good anatomical area revascularization (resulting in local intake of antibiotics) and the biomimetism of HA prosthesis. Also, Johnson et al. reported a case of infection of HA cement cranioplasty successfully salvaged without removal of the implant, and Zanotti et al. described a case of a conservative treatment of infection of a custom-made porous HA cranioplasty implant, with no problems to the implant at a follow-up of 6 years [25, 50]. Quite surprisingly, the conservative option was also recently exploited for titanium cranioplasty [22], though metal has no biomimetic properties.

Although conservative treatment aims to the salvage of the cranioplasty, recent awareness on the biofilm formation should be kept in mind. The biofilm is an organized community of bacteria attached to surfaces, including implanted medical devices and host mucosal tissues, embedded in a slime-like matrix composed of polysaccharides, nucleic acids and proteins known as extracellular polymeric substances developmental. Formation of biofilm includes five stages: reversible attachment, irreversible adhesion, aggregation, growth and maturation and detachment. Potentially, all species of bacteria may form biofilm. It would be responsible for recurrent infections or chronic inflammation in the absence of patent infection, due to the immune response of the host. This is particularly interesting since this immune response could be also partly responsible of the resorption of autologous bone flap, as biofilm has been identified in cryopreserved autologous bone in spite of negative microbiological cultures at the time of implantation [8].

Moreover, to optimize the management of biofilm-associated infections, a prompt and correct diagnosis should be made. Thus, sonication of removed implant components and prolonged incubation of cultures is recommended [15].

On these grounds, Conen et al. proposed to manage cranioplasty infections by subdividing the cases in early and delayed/late ones, according to the onset of infection before or after 4 weeks from the cranioplasty implantation. This results in the presence, respectively, of an "immature" or "mature" biofilm. Further data to drive the treatment come from the availability of anti-biofilm therapy.

If the microorganism is known and susceptible to anti-biofilm therapy, salvage of the prosthesis may be attempted in early infections. Surgery is followed by a 12-week anti-biofilm therapy. If the microorganism is not susceptible to anti-biofilm therapy, implant removal is required and reinsertion is possible usually after 6 weeks of postoperative antibiotic treatment [15].

In the decision-making process, clinical findings may play a crucial role, as well as radiological features (lytic areas and bony changes, intra-parenchymal or enhancing epi- or subdural collection of fluid, subgaleal collections and/or soft tissue swelling) [5]. An isolated soft tissue involvement may motivate to begin a more conservative treatment, although some authors argue that it is not possible to distinguish between superficial and deep wound infections, due to their contiguity after surgery [15].

However, although there is relatively scant literature describing the role of biofilm in neurosurgical infections, it is becoming increasingly fair that biofilm plays an important role in postoperative infections involving neurosurgical devices.

This evidence would be in favour of more aggressive treatment of cranioplasty-associated infection, based on the removal of cranioplasty itself. This approach warrants more reliable and faster cure of the infection, but it opens other questions, in particular concerning the timing of redo cranioplasty. On these grounds, most surgeons tend to consider an implant-free interval of at least 6–12 months, in order to reduce the risk of re-infection [4, 11, 13, 37], though there is no agreement on timing for redo cranioplasty which is often dictated by clinical and radiological evidence of infection resolution. This is extremely important, considering the need to balance the risk of functional consequences of craniectomy (CSF dynamics alteration, lack of protection of the cerebral parenchyma and trephined syndrome) [15] and the necessity to wait for reducing the risk of recurrent infection.

Only a few studies partially address such a topic [26, 36], though paper dealing with this issue in paediatric population lacks in the literature so far. The necessity of complete antimicrobial treatment along with clinical and laboratory assessments that rule out persisting infection of the wound and soft tissues is generally accepted. After complete resolution of the infection, some authors prefer a more conservative approach waiting at least 6 months for redo cranioplasty [26] whilst others suggest a more aggressive behaviour reducing the aforementioned time to 3–4 months [36], without significant differences in complications compared to late-stage implant-based cranioplasty reconstruction.

Finally, the material selection in redo cranioplasty deserves further attention. Available materials include acrylics (polymethylmethacrylate, PMMA), metals (titanium), plastic polymers (porous polyethylene and polyetheretherketone, PEEK) and ceramics (hydroxyapatite, HA) [18]. No materials are free of complications, and in particular infections. Some studies have shown the higher risk of infections for PMMA than titanium mesh and HA [33, 46, 49, 50]. The effort of future research should aim to enhance the antimicrobial effect of inert materials [2, 36, 44]. One paper suggests the use of vancomycin and tobramycin-impregnated PMMA. Tobramycin is a bactericidal aminoglycoside antibiotic with broad Gram-negative and Gram-positive coverage whilst Vancomycin is a glycopeptide antibiotic with both bactericidal and bacteriostatic activity. Such a choice is intriguing being those antibiotics quite effective against the more common pathogens of cranioplasty infection [21]. Nonetheless, PMMA has several drawbacks in paediatric population [18]. Other authors suggest the use of vancomycin powder topically instilled during surgery but no evidence of a clear reduction in infection risk are reported [1, 6].

Prevention

Taking into account the morbidity and costs of cranioplasty infection, every effort must be taken in preventing it. Prevention starts from a clear understanding of the risk factors for cranioplasty infection.

As for the previously discussed paragraph, several potential risk factors are reported throughout the literature even though, for some of them, there is no consensus.

Most of the risk factors are non-modifiable and are connected either with the dynamic of the prior cerebral insult that requires craniectomy either with patient clinical condition. In fact, risk factors are considered history of preoperative radiation, previous infection, frontal location with sinus involvement [1, 37, 38, 42], motor deficits, GCS < 4, lower heamoglobin levels, hydrocephalus, recent systemic infection [27, 40], hemorrhagic stroke, older age [30, 37, 48], patient morbidity and evidence of preoperative subgaleal collection [24, 26, 29, 37].

On the other hand, some conditions may benefit from careful planning of the craniectomy and of the subsequent cranioplasty. Among them, there are the need for large craniectomy and subsequent large cranioplasty [30, 37, 48], the overuse of coagulation during cranioplasty procedure impairing healing of the wound [51], the length of the operative time, the choice to resect temporalis muscle and wound breakdown [24, 26, 29, 37]. Lastly, some literature reports suggest that performing cranioplasty in a different hospitalization than the one in which craniectomy was performed can reduce the risk of infection. These evidences are supposedly linked to the resolution with time of the local inflammation offering a safer surgical bed [27, 40]. However, the recovery of general conditions with more efficient immune response and the resolution or reduction of microbiological skin contamination after hospital discharge should be also considered.

Similarly, some authors stated that late cranioplasty may reduce the risk of infection [29–31]. However, the relationship between the timing of cranioplasty and the risk of infection remains debated. Indeed, other authors failed to find significant difference in infection rates between early and late cranioplasty [32]. On the other hand, early cranioplasty, performed as the brain edema has normalized, may contribute to a better neurological outcome [33], also reducing the risk of CSF-related complications with the need for additional hospital admissions and subsequent risk of perioperative infections [34]. Another argument in favour of early cranioplasty is the easier dissection plane during the operative procedure. This reduces the operative time and the risk of postoperative complications such as subgaleal collections that may favour infection of the cranioplasty [35]. Moreover, in young children, an early cranioplasty has the advantage of restoring the symmetrical skull growth, especially in the first years of life [17], thus reducing the risk of failure and the need for redo cranioplasty.

Another controversial risk factor for cranioplasty infection regards the management of hydrocephalus, if present at the time of cranioplasty. Most of the papers suggest an increased infection risk whenever the two procedures are carried on at the same time [35, 39, 45, 47]. Possibly, such a data are connected with the longer surgical time and the use of multiple non-biological hardware. On the other hand, other authors failed to confirm differences in infection rates [34, 41].

Finally, it is widely accepted that prevention of complications passes through the careful standardization of the surgical procedure, in order to avoid any possible contamination. The role of bundle in reducing the risk of infection when implanting neurosurgical devices has been already proven through the literature [14]. Similarly, operative bundles for cranioplasty have been proposed [28, 31]. In particular, Le et al. suggested the use of perioperative Vancomycin (4 doses), a barrier dressing through postoperative day, and decolonization of the surgical incision using topical chlorhexidine after surgery [28]. The bundle proposed by Liu et al. consists of depilatory agents for skin preparation before the operative procedure instead of razor shaving; preoperative prophylaxis with Cefuroxime (1.5 g); Vancomycin for patients with previous staphylococcal infection; use of alcohol-based hand rub instead of conventional surgical scrub before surgery; and custom-made titanium mesh to reconstruct cranial defect. After the operation, physicians wore gloves to change the wound dressing and patients received a dressing for 3 days after the

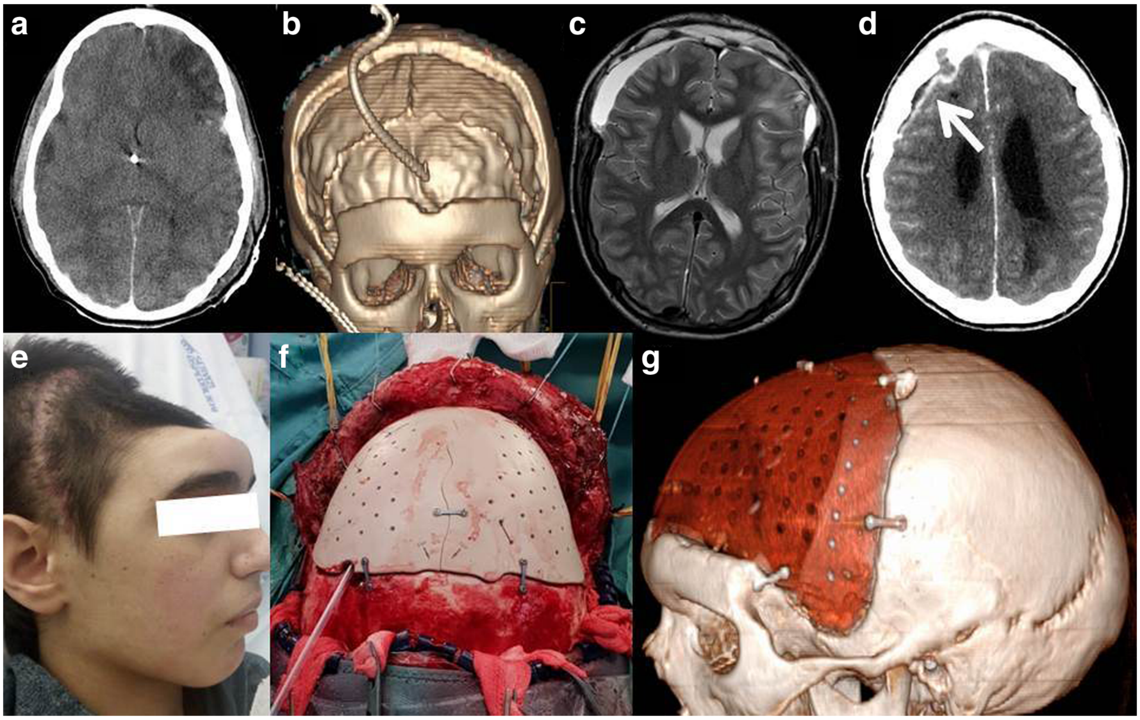

Fig. 2 Severe head injury with massive brain swelling (**a**), requiring bifrontal craniectomy (**b**) with resolution of brain oedema (**c**) and subsequent autologous cranioplasty that was complicated by multi-resistant Acinetobacter baumannii infection (**d**, arrow). After removal of the bone flap and surgical toilette, antibiotic therapy with intravenous colistin and tygeciclin was administered for 6 weeks. Patient developed severe sinking flap syndrome (**e**). Thus, redo cranioplasty with PEEK implant was performed 2 months after the end of the antibiotic therapy (**f** and **g**) with good neurological recovery

surgery and then had daily topical chlorhexidine wound decolonization for 3 days or until hospital discharge [31]. A bundle specific for paediatric population, with its peculiar features, is still lacking so far.

Additionally, literature data on the management of patients contaminated by multi-resistant germs undergoing cranioplasty are completely lacking, although there is great concern about this topic. Indeed, neurosurgeons have to face more and more frequently with this condition resulting from the ever-growing capability to treat complex patients after catastrophic head injury and the increasing issue of multi-resistant germ infection and colonization in medical setting.

Institutional bundle

In patients undergoing cranioplasty, we still prefer complete hair shaving with clippers, differently from all the other neurosurgical procedures that are routinely performed without shaving. This allows to identify areas of skin dehiscence or breakdown that may negatively affect the outcome of cranial repair. Each patient with history of systemic infection during the hospital stay or skin contamination by multi-resistant germ receives infectious disease counselling before cranial repair. Chlorhexidine shower the night before surgery is performed. This measure is started several days before surgery in case of skin contamination by multi-resistant microorganisms.

Standard antibiotic prophylaxis is done with Cefazolin 30 mg/kg, before skin incision, eventually repeated if surgery is prolonged over 4 h, in accordance with the American Society of Health-System Pharmacists (ASHP) guidelines, except for patients with beta-lactam antibiotic allergy or with known colonization or high risk of colonization by Methicillin-resistant *Staphylococcus aureus* (MRSA) [7]. In these cases, Vancomycin 20 mg/kg is started 2 h before surgery, with infusion lasting 90 min.

In case of colonization by extensively drug-resistant micro-organism (XDR), an antibiotic chosen according to the antibiogram is administered before surgery in addition to Vancomycin. Antibiotic therapy is prolonged 24 h after surgery, though this approach is not evidence-based but empirical. Intraoperative disinfection is carried on with 2% *w*/*v* chlorhexidine gluconate (CHG) in 70% *v*/*v* isopropyl alcohol (IPA) solution. The existing surgical wound is reopened, minimizing the use of coagulation. Implant is soaked in antibiotic solution (Gentamicin) if recommended by the manufacturer, since also this measure is empirical. The new implant is secured to the bone with sutures in younger children and with titanium plates in the elder. The wound is then closed with monofilament non-resorbable sutures. External subcutaneous or subgaleal drainage is avoided, whenever feasible. If hydrocephalus coexists, perioperative external ventricular antibiotic-impregnated catheter is placed and the implantation of internal shunt is postponed. Attention is paid to place the external ventricular drainage contralateral to the cranioplasty site, or at least as distant as possible. Sutures are removed after 15 days.

Cranioplasty infection is ascertained with clinical, laboratory and radiological evaluation. White blood count, CRP and procalcitonin are evaluated together with contrast-enhanced CT scan in most cases. MRI with DWI sequences may further investigate doubtful cases. In case of cranioplasty infection, the infected flap is removed along with all the synthetic materials present in the surgical bed (e.g. sutures, dural graft…). Several samplings are performed for microbiological cultures and antibiogram. Broad-spectrum antibiotics, active against both Gram-positive and Gram-negative bacteria, are promptly started. Thereafter, it is simplified or modified according to microbiological results and prolonged for 6–8 weeks, until normalization of the laboratory and radiological exams. If radiological exams show sign of osteomyelitis, antibiotic therapy continues up to 12 weeks.

After infection resolution, at least 3-month interval is waited for redo cranioplasty. This interval is sufficient for ruling out persisting or recurrent local infection. Then, CT scan with contrast administration is performed. This exam allows us to exclude subtle persisting infectious collections and to manufacture the customized implant. Material for redo cranioplasty is chosen according to several features. In general, whenever feasible, osteo-integrative solutions, as macroporous HA, are preferred. If the complex geometry of the defect or the young age of the patient, namely under 2 years, contraindicate, this solution PEEK is preferred. Timing for redo cranioplasty is usually decided according to systemic, local and neurological conditions of the patient. Exceptionally, redo cranioplasty has been performed before 3 months in case of severe sunken flap syndrome (Fig. 2). In redo cranioplasty, perioperative measures are similar to first-line cranioplasty.

Conclusions

Infectious complications of cranioplasty may have a high economical and clinical burden, in particular, in children. A thorough knowledge and understanding of risk factors for infection may lead to surgical strategies and bundles, aiming to reduce this kind of complication. The timing of cranioplasty and choice of the material obviously affect and are affected by the risk of infection. Thus, innovation in materials used for cranial repair should also aim to enhance the antimicrobial properties of these inert materials.

Compliance with ethical standards

Conflict of interest There are no conflict of interests to disclose.

References

1. Abode-Iyamah KO, Chiang H-Y, Winslow N, Park B, Zanaty M, Dlouhy BJ, Flouty OE, Rasmussen ZD, Herwaldt LA, Greenlee JD (2018) Risk factors for surgical site infections and assessment of vancomycin powder as a preventive measure in patients undergoing first-time cranioplasty. J Neurosurg 128(4):1241–1249
2. Albanese A, De Bonis P, Sabatino G, Capone G, Marchese E, Vignati A, Maira G (2009) Antibiotic-impregnated ventriculo-peritoneal shunts in patients at high risk of infection. Acta Neurochir 151(10):1259–1263
3. Auguste KI, McDermott MW (2006) Salvage of infected craniotomy bone flaps with the wash-in, wash-out indwelling antibiotic irrigation system. Technical note and case series of 12 patients. J Neurosurg 105(4):640–644
4. Baumeister S, Peek A, Friedman A, Levin LS, Marcus JR (2008) Management of postneurosurgical bone flap loss caused by infection. Plast Reconstr Surg 122(6):195e–208e
5. Bhaskar IP, Inglis TJJ, Lee GYF (2014) Clinical, radiological, and microbiological profile of patients with autogenous cranioplasty infections. World Neurosurg 82(3–4):e531–e534
6. Bokhari R, You E, Zeiler FA, Bakhaidar M, Bajunaid K, Lasry O, Baeesa S, Marcoux J (2019) Effect of intrawound vancomycin on surgical site infections in nonspinal neurosurgical procedures: a systematic review and meta-analysis. World Neurosurg 123:409–417.e7
7. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA, American Society of Health-System Pharmacists, Infectious Disease Society of America, Surgical Infection Society, Society for Healthcare Epidemiology of America (2013) Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 70(3):195–283
8. Braxton EE, Ehrlich GD, Hall-Stoodley L, Stoodley P, Veeh R, Fux C, Hu FZ, Quigley M, Post JC (2005) Role of biofilms in neurosurgical device-related infections. Neurosurg Rev 28(4):249–255
9. Brommeland T, Rydning PN, Pripp AH, Helseth E (2015) Cranioplasty complications and risk factors associated with bone flap resorption. Scand J Trauma Resusc Emerg Med 23:75
10. Buang SS, Haspani MS (2012) Risk factors for neurosurgical site infections after a neurosurgical procedure: a prospective observational study at Hospital Kuala Lumpur. Med J Malaysia 67(4):393–398
11. Chang V, Hartzfeld P, Langlois M, Mahmood A, Seyfried D (2010) Outcomes of cranial repair after craniectomy. J Neurosurg 112(5):1120–1124
12. Cheng Y-K, Weng H-H, Yang J-T, Lee M-H, Wang T-C, Chang C-N (2008) Factors affecting graft infection after cranioplasty. J Clin Neurosci 15(10):1115–1119
13. Chiang H-Y, Kamath AS, Pottinger JM, Greenlee JDW, Howard MA, Cavanaugh JE, Herwaldt LA (2014) Risk factors and outcomes associated with surgical site infections after craniotomy or craniectomy. J Neurosurg 120(2):509–521

14. Choux M, Genitori L, Lang D, Lena G (1992) Shunt implantation: reducing the incidence of shunt infection. J Neurosurg 77(6):875–880
15. Conen A, Fux CA, Vajkoczy P, Trampuz A (2017) Management of infections associated with neurosurgical implanted devices. Expert Rev Anti-Infect Ther 15(3):241–255
16. Coulter IC, Pesic-Smith JD, Cato-Addison WB, Khan SA, Thompson D, Jenkins AJ, Strachan RD, Mukerji N (2014) Routine but risky: a multi-centre analysis of the outcomes of cranioplasty in the northeast of England. Acta Neurochir 156(7): 1361–1368
17. De Bonis P, Frassanito P, Mangiola A, Nucci CG, Anile C, Pompucci A (2012) Cranial repair: how complicated is filling a “hole”? J Neurotrauma 29(6):1071–1076
18. Feroze AH, Walmsley GG, Choudhri O, Lorenz HP, Grant GA, Edwards MSB (2015) Evolution of cranioplasty techniques in neurosurgery: historical review, pediatric considerations, and current trends. J Neurosurg 123(4):1098–1107
19. Girgis F, Walcott BP, Kwon C-S, Sheth SA, Asaad W, Nahed BV, Eskandar EN, Coumans J-V (2015) The absence of fever or leukocytosis does not exclude infection following cranioplasty. Can J Neurol Sci 42(4):255–259
20. Honeybul S, Ho KM (2016) Cranioplasty: morbidity and failure. Br J Neurosurg 30(5):523–528
21. Hsu VM, Tahiri Y, Wilson AJ, Grady MS, Taylor JA (2014) A preliminary report on the use of antibiotic-impregnated methyl methacrylate in salvage cranioplasty. J Craniofac Surg 25(2):393–396
22. Hu Y, Li X, Zhao R, Zhang K (2018) Conservative treatment for delayed infection after cranioplasty with titanium alloy. J Craniofac Surg 29(5):1258–1260
23. Iaccarino C, Mattogno PP, Zanotti B, Bellocchi S, Verlicchi A, Viaroli E, Pastorello G, Sgulò F, Ghadirpour R, Servadei F (2018) Septic complication following porous hydroxyapatite cranioplasty: prosthesis retention management. J Neurosurg Sci 62(6):765–772
24. Jin S-W, Kim S-D, Ha S-K, Lim D-J, Lee H, You H-J (2018) Analysis of the factors affecting surgical site infection and bone flap resorption after cranioplasty with autologous cryopreserved bone: the importance of temporalis muscle preservation. Turk Neurosurg 28(6):882–888
25. Johnson PJ, Robbins DL, Lydiatt WM, Moore GF (2000) Salvage of an infected hydroxyapatite cement cranioplasty with preservation of the implant material. Otolaryngol Head Neck Surg 123(4):515–517
26. Kim T, Han JH, Kim HB, Song K-H, Kim ES, Kim Y-H, Bang JS, Kim C-Y, Oh CW (2013) Risk factors of surgical site infections after supratentorial elective surgery: a focus on the efficacy of the wound-drain-tip culture. Acta Neurochir 155(11):2165–2170 discussion 2170
27. Kimchi G, Stylianou P, Wohl A et al (2016) Predicting and reducing cranioplasty infections by clinical, radiographic and operative parameters - a historical cohort study. J Clin Neurosci 34:182–186
28. Le C, Guppy KH, Axelrod YV, Hawk MW, Silverthorn J, Inacio MC, Akins PT (2014) Lower complication rates for cranioplasty with peri-operative bundle. Clin Neurol Neurosurg 120:41–44
29. Lee C-H, Chung YS, Lee SH, Yang H-J, Son Y-J (2012) Analysis of the factors influencing bone graft infection after cranioplasty. J Trauma Acute Care Surg 73(1):255–260
30. Li A, Azad TD, Veeravagu A, Bhatti I, Long C, Ratliff JK, Li G (2017) Cranioplasty complications and costs: a national population-level analysis using the MarketScan Longitudinal Database. World Neurosurg 102:209–220
31. Liu H, Dong X, Yin Y, Chen Z, Zhang J (2017) Reduction of surgical site infections after cranioplasty with perioperative bundle. J Craniofac Surg 28(6):1408–1412
32. Malcolm JG, Mahmooth Z, Rindler RS, Allen JW, Grossberg JA, Pradilla G, Ahmad FU (2018) Autologous Cranioplasty is associated with increased reoperation rate: a systematic review and meta-analysis. World Neurosurg 116:60–68
33. Matsuno A, Tanaka H, Iwamuro H, Takanashi S, Miyawaki S, Nakashima M, Nakaguchi H, Nagashima T (2006) Analyses of the factors influencing bone graft infection after delayed cranioplasty. Acta Neurochir 148(5):535–540 discussion 540
34. Meyer RM, Morton RP, Abecassis IJ, Barber JK, Emerson SN, Nerva JD, Ko AL, Chowdhary MC, Levitt MR, Chesnut RM (2017) Risk of complications with simultaneous cranioplasty and placement of ventriculoperitoneal shunt. World Neurosurg 107: 830–833
35. Mustroph CM, Malcolm JG, Rindler RS, Chu JK, Grossberg JA, Pradilla G, Ahmad FU (2017) Cranioplasty infection and resorption are associated with the presence of a ventriculoperitoneal shunt: a systematic review and meta-analysis. World Neurosurg 103:686–693
36. Oei JD, Zhao WW, Chu L, DeSilva MN, Ghimire A, Rawls HR, Whang K (2012) Antimicrobial acrylic materials with in situ generated silver nanoparticles. J Biomed Mater Res B Appl Biomater 100(2):409–415
37. Piazza M, Grady MS (2017) Cranioplasty. Neurosurg Clin N Am 28(2):257–265
38. Reddy S, Khalifian S, Flores JM, Bellamy J, Manson PN, Rodriguez ED, Dorafshar AH (2014) Clinical outcomes in cranioplasty: risk factors and choice of reconstructive material. Plast Reconstr Surg 133(4):864–873
39. Rocque BG, Agee BS, Thompson EM, Piedra M, Baird LC, Selden NR, Greene S, Deibert CP, Hankinson TC, Lew SM, Iskandar BJ, Bragg TM, Frim D, Grant G, Gupta N, Auguste KI, Nikas DC, Vassilyadi M, Muh CR, Wetjen NM, Lam SK (2018) Complications following pediatric cranioplasty after decompressive craniectomy: a multicenter retrospective study. J Neurosurg Pediatr 22(3):225–232
40. Rosseto RS, Giannetti AV, de Souza Filho LD, Faleiro RM (2015) Risk factors for graft infection after cranioplasty in patients with large hemicranial bony defects. World Neurosurg 84(2):431–437
41. Schuss P, Borger V, Güresir Á, Vatter H, Güresir E (2015) Cranioplasty and ventriculoperitoneal shunt placement after decompressive craniectomy: staged surgery is associated with fewer postoperative complications. World Neurosurg 84(4):1051–1054
42. Still M, Kane A, Roux A, Zanello M, Dezamis E, Parraga E, Sauvageon X, Meder J-F, Pallud J (2018) Independent factors affecting postoperative complication rates after custom-made porous hydroxyapatite cranioplasty: a single-center review of 109 cases. World Neurosurg 114:e1232–e1244
43. Tamaki T, Eguchi T, Sakamoto M, Teramoto A (2004) Use of diffusion-weighted magnetic resonance imaging in empyema after cranioplasty. Br J Neurosurg 18(1):40–44
44. Tamburrini G, Massimi L, Caldarelli M, Di Rocco C (2008) Antibiotic impregnated external ventricular drainage and third ventriculostomy in the management of hydrocephalus associated with posterior cranial fossa tumours. Acta Neurochir 150(10): 1049–1055 discussion 1055-1056
45. Tsang AC-O, Hui VK-H, Lui W-M, Leung GK-K (2015) Complications of post-craniectomy cranioplasty: risk factor analysis and implications for treatment planning. J Clin Neurosci 22(5): 834–837

46. van de Vijfeijken SECM, Münker TJAG, Spijker R, Karssemakers LHE, Vandertop WP, Becking AG, Ubbink DT, CranioSafe Group (2018) Autologous bone is inferior to alloplastic cranioplasties: safety of autograft and allograft materials for cranioplasties, a systematic review. World Neurosurg 117:443–452.e8
47. Yang NR, Song J, Yoon K-W, Seo EK (2018) How early can we perform cranioplasty for traumatic brain injury after decompressive craniectomy? A retrospective multicenter study. World Neurosurg 110:e160–e167
48. Zanaty M, Chalouhi N, Starke RM et al (2014) Predictors of infections following cranioplasty: a retrospective review of a large single center study. ScientificWorldJournal 2014:356042
49. Zanotti B, Zingaretti N, Verlicchi A, Robiony M, Alfieri A, Parodi PC (2016) Cranioplasty: review of materials. J Craniofac Surg 27(8):2061–2072
50. Zanotti B, Zingaretti N, Verlicchi A, Alfieri A, Parodi PC (2018) Successful strategies for dealing with infected, custom-made hydroxyapatite cranioplasty. J Craniofac Surg 29(5):1127–1131
51. Zheng W-J, Li L-M, Hu Z-H, Liao W, Lin Q-C, Zhu Y-H, Lin S-H (2018) Excessive hemostasis on the scalp increases superficial surgical site infection rate in cranioplasty. World Neurosurg 120:e811–e817
52. Zierdt CH (1983) Evidence for transient Staphylococcus epidermidis bacteremia in patients and in healthy humans. J Clin Microbiol 17(4):628–630