CHAPTER 1

Revision Surgery in the Lower Limb of Haemophilic Patients

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Abstract: The management of a failed orthopaedic implant is potentially complex in haemophilic patients. Several critical aspects have to be considered ranging from a tailored haematological care and rehabilitative period to high technically demanding surgical procedures and type of implants needed for the management of the compromised joint. Hip and knee are the most involved joints needing a substitution after a prosthetic failure. All these interventions are delicate and expensive, particularly when the failure is not a simple aseptic loosening but it is represented by an infection or a case with severe bone defects, pseudotumours, and soft tissue mortification. Only specific facilities and specialized teams may be able to manage such these conditions in a safe manner.

Keywords: Ankle arthroplasty, Aseptic loosening, Haemophilia, Hip arthroplasty, Infection, Knee arthroplasty, Revision, Salvage surgery.

INTRODUCTION

A *revision* is defined as the substitution of one or more components of a failed orthopaedic implant. Several mechanisms may induce a failure of a prosthesis, and then needing a revision. The most frequent causes of failure are: aseptic loosening and wear, infection, and instability. Lower more than upper limbs are affected by these clinical issues [1 - 5]. During last decades, given the increasing mean age of the population and the consequent more active general way of life, we are assisting to a worsening of chronic diseases. This is particularly true for

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degenerative articular pathologies as Osteoarthritis, specifically in hips and knees. The result is that a larger number of surgical procedures (primary total hip and knee arthroplasties) have been recently performed worldwide with respect to the past [1, 4 - 6]. The more the number of procedures, the more the rate of complications: an increasing number of failures are consequently expected [6, 7].

In the haemophilic population, a joint replacement is generally performed in very young patients, often less than 40 years old. In this setting and differently from adult-elderly subjects affected by Osteoarthritis, the main mechanism of failure of an orthopaedic implant has been considered the septic loosening [8 - 13] (Fig. **1**).

Fig. (1). Comparison between the classic radiologic aspect of a failure of primary cemented knee implants in patients affected by Osteoarthritis (a: aseptic loosening in a 74 years-old female) and Haemophilic arthropathy (b: septic loosening in a 53-years old male).

Several generations of haemophiliacs suffered for infections after orthopaedic procedures with dramatic rates of incidence reported in different series [8, 9, 11, 12]. The second common cause of failures is represented by the aseptic loosening related to bleedings after surgery [8, 9, 11, 12, 14 - 17](Fig. **2**).

No clear data are reported regarding wear and pure mechanical failures. Differently from the past, the modern evaluation of clinical results is based not only on relief from symptoms and restoration of functional ability but also on the longest survivorship of the implants. Thus, it would be necessary to consider also the survival rates of orthopaedic implants in very young patients [18].

Fig. (2). Typical radiologic aspect of a TKA in a 42 years-old haemophilic patient **(a)** failed after recurrent bleedings 4 years after the index operation **(b)** . Of noting, the cemented femoral component and tibial baseplate, and the cementless tibial keel and stem. This is the modern ideal fixation of components in young haemophilic patients.

RISK FACTORS & CLINICAL SETTINGS

As mentioned, most failures in Haemophilia are related to infections more than aseptic loosening or instability. Several factors are likely involved: a higher prevalence of pre-existing joint damage due to recurrent haemarthrosis before surgery; the consistent risk of subclinical haemarthroses in subjects after a joint replacement; and the growing number of joint replacements performed in this population in the last decades. Historically, co-infections in haemophilic patients have been addressed as important risk factors [19 - 27]. Most failures have been related to co-infections in patients treated by clotting factor products before 1990. The main co-infections have been represented by hepatitis B and C, and HIV. Hepatitis B and C seem nowadays not to be significant as potential infectious risks, despite the prevalence of hepatitis C has been reported as 80–100% in the haemophilic population and in about 80% of these subjects a chronic hepatitis developed [20 - 23]. HIV infection is considered a strong risk factor for septic sequelae in Haemophilia. Ragni *et al.* reported a survey on the US haemophilia centers to determine the incidence of postoperative infections in HIV-positive haemophiliacs with CD4 counts of $\leq$200 mm^3 undergoing orthopaedic surgery.

Among 115 centers a postoperative infection occurred in 10 (15.1%) of 66 patients undergoing 74 orthopaedic procedures within 6 months following surgery [24]. Joint arthroplasty has shown a 10 times higher risk of postoperative infection with respect to other forms of surgery (arthroscopy, osteotomy, joint fusion) with a percentage of 26.5% *vs.* 2.5%. Phillips *et al.* similarly reported a higher risk of postoperative bacterial and opportunistic infections in HIV-positive haemophilic patients undergoing orthopaedic surgery: however no significant difference between the number of CD4 lymphocyte in HIV-positive patients undergoing surgery was found when compared to HIV-positive subjects not undergoing surgery [25]. Moreover, the overall rate of prosthetic joint infection after arthroplasty in haemophiliacs especially if HIV-positive has been reported as higher than the non-haemophilic population [23, 26 - 29]. Thomason *et al.* published a series of 15 HIV-positive haemophiliacs undergoing 23 TKAs with 4 infective failures (2 early, 2 late) at a mean follow-up of 7.5 years [26]. Rodriguez-Merchan and Wiedel reported their series of 26 HIV-positive patients (37 TKAs) with at least 200mm^3 CD4 count at a mean follow-up of 9.6 years. They recorded a total of 28 complications, with 5 failures related to infections (one case of a superficial infection managed by irrigation, antibiotics, and debridement; three deep infections treated by major surgery) and 2 two aseptic loosening [27]. Ashrani *et al.* reported an overall incidence rate of joint infections of 83/100.000 cases per year in a 7-years period, ranging from 26 to 129 cases per 100,000 person-years annually. The incidence of septic arthritis in haemophilic patients was 15–40 times higher than the reported incidence in the general population, 3–4 times higher than Rheumatoid Arthritis, and similar to that reported in patients with prosthetic joints [28]. Unger *et al.* reported about their series of 15 patients (26 TKAs) affected by HIV that at a mean follow-up of 6.4 years presented a high rate of complications (haemarthrosis, stiffness, varus or valgus deformity, inhibitors development) but no septic loosening [29]. It is nowadays accepted that a very symptomatic and altered joint arthropathy in HIV-positive patients with a CD4 count of ≥200mm^3 and a not conclamate AIDS should be the minimum criteria to plan a major orthopaedic procedure [23, 30]: respecting these indications, a clinical success is expected without an increased risk for complications similar to haemophiliacs without co-infections [15].

Haemophilia type-A is more severe than type-B in terms of bleeding rate, development of inhibitors, progression of the arthropathy, and severity of symptoms [31 - 34]. Similarly, subjects affected by Haemophilia A seems to be prone to develop more severe arthropathies and a higher number of postoperative complications after orthopaedic surgery with respect to Haemophilia B [7, 11, 12, 32]. Moreover, patients with Haemophilia A showed a lesser survivorship due to a higher rate of complications compared to Haemophilia B subjects [32].

Fig. (3). Primary TKA in a 37 years-old haemophiliac with all cemented components **(a)** . Nine years after surgery, severe aseptic failure with gross instability and formation of pseudotumours on the distal femur and the metadiaphyseal portion of tibia.

Haemophilic patients with inhibitors are mostly prone to develop complications (haemarthrosis, aseptic and septic loosening) after an arthroplasty compared to haemophiliacs without inhibitors since a higher tendency to undergo bleedings [7, 31, 35, 36]. Recurrent postoperative bleedings and permanence of free blood in an operated joint may induce two different mechanisms of failure. Blood and its components may activate an acute inflammation with involvement of cells and cytokines acting as trigger for bone resorption at the bone-component counterface. This may lead to osteolysis and early loosening of the implant [11, 12, 31]. This condition usually realizes with a typical interval of months, characterized by persisting and increasing pain, functional limitation, perceived instability, and necessity of devices as crutches or canes. In haemophilic subjects, a specific pattern of aseptic failure of an implant is the formation of *pseudotumours*, masses characterized by areas of destructured bone and fibrous tissue in bone segments

(femur, tibia) close to the prosthetic components. This is the result of recurrent bleedings or persistency of blood in zones of osteolysis in which inflammation does not resume. In such these cases, components loosening realizes and periprosthetic bone becomes weak not able to support the weightbearing. Patients complain pain and progressive functional impairment, needing support by devices as canes or crutches earlier than a simple loosening (Fig. **3**).

On the other side, blood in a joint is an ideal pabulum for bacterial contamination, thus an infection may develop inducing a septic failure. Generally, a TKA or THA infection in haemophilic patients does not differ from non-haemophilic patients. However, if it occurs in HIV co-infected haemophiliacs, serious life-threatening conditions characterized by a septic status may realize [29]. The time interval of such this complication is variable from days to months, depending on the acute, subacute, or chronic onset of the joint infection [29, 36]. Moreover, in a small percentage of haemophilic patients it is not uncommon that a knee or hip deep infection may quickly evolve in a severe compromission of soft tissues, with a large swelling, a sinus tract, and even skin necrosis. An infected pseudotumour may add a further complication in an already severe clinical setting (Fig. **4**).

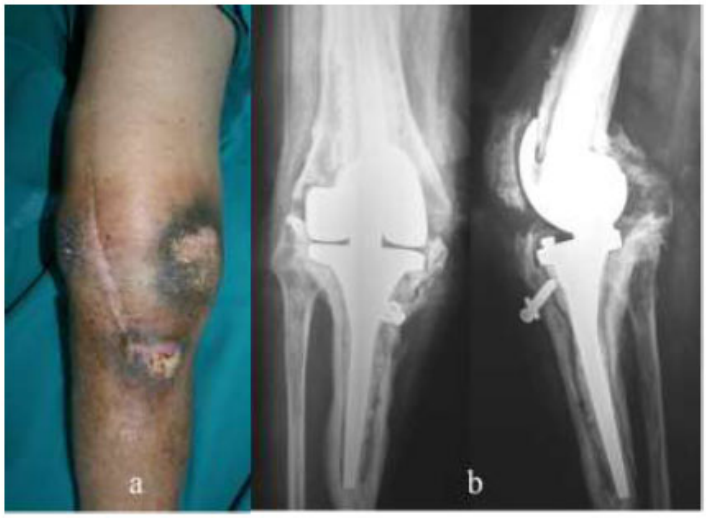

Fig. (4). Clinical **(a)** and radiographic **(b)** aspects of an infected cemented primary TKA with long stems and high constraint in a 53-years old male affected by severe Haemophilia A with high-titre inhibitors. To note the severe soft tissue mortification and the active sinus tract.

Recent studies have found that blacks, hispanics and age >30 years were associated with increased risk for septic arthritis among patients with Haemophilia. The reasons for these differences are not to date entirely clear, but it is possible that minorities have decreased access to health care compared with whites and may also undergo to a delay in seeking medical attention for either haemarthrosis or localized or systemic infection. Moreover, Hispanics and blacks generally have a worse functional status than Caucasians across all ages regardless of inhibitor status [37 - 39]. These may represent a further risk factor for complications after a joint replacement, and has to be kept in mind by the Haemophilia teams.

Finally, immune modulated and biologic therapies have been recently introduced to control HIV or to induce a negativization of hepatitis C [40]. In case of a joint replacement, subjects should be consider the risk of infections facing these treatments. A multidisciplinary evaluation, a clear and specific informed consent, and a strict control by the orthopaedic surgeon, haematologist, and infectious disease specialist should be strongly considered to prevent or to detect early complications.

DIAGNOSTIC ASPECTS

Diagnosis of a THA or TKA failure in haemophiliacs is performed as for other orthopaedic patients. Clinical signs, blood examinations, synovial fluid analysis, imaging, and exclusion of other causes are generally sufficient to confirm the suspect and to plan a revision. Radiolucent lines and areas of osteolysis should be evaluated and detected by a standard radiographic follow-up (usually 1-3-6-12 months after surgery; then yearly evaluation). The presence of not or slowly progressive radiolucency zones have been reported in several series around acetabular cups, femoral stems, or femoral and tibial components [7, 11, 41, 42] at a mean follow-up of less than 10 years. Mostly of these reported radiographic alterations were asymptomatic and few cases effectively needed a revision.

In case of pseudotumours, a MRI with contrast or a bone scan by marked leucocytes is suggested to exclude any actual tumoral condition, given the particular cancer-like aspect of most masses around hips and knees. A further

biopsy in specific cases may be indicated as an exclusion criteria.

TREATMENT OPTIONS

As mentioned, despite the presence of radiolucent lines and osteolysis in several series after a THA or TKA at the mid- to long-follow-up, mostly of the haemophilic patients do not complain symptoms or actually need any revision of their implants. In such cases, it is reasonable a more strict radiographic and orthopaedic evaluation to detect any further worsening. Some cases may benefit of the brand new strategies that are arising in the last years and associated with encouraging results despite there is still lack of full evidence. Examples of these treatments are pharmacological substances acting as promoter of bone metabolism [43] and the physical therapy improving the local bone metabolism in the sense of ingrowth more than resorption [44].

In case of significant progressive radiolucencies or severe osteolysis associated with symptoms, revision surgery is mandatory, particularly in younger subjects. In most cases, by a close cooperation between haematologists and orthopaedics, and a tailored haematological treatment, it is possible to perform a revision similarly to a standard revision. Furthermore, general perioperative risks are fewer given the young mean age of the subjects candidate to this procedure.

Three are the most common settings of failures of an implant of the lower limb in haemophilic patients: the aseptic loosening related to recurrent bleedings; the septic loosening; and the severe failure with soft tissue mortifications associated or not with pseudotumours. The following is a brief overview of these specific cases.

In case of an aseptic failure, revision of one or more component is required. The use of modular knee and hip systems have recently simplified this condition. However, old generation implants as used during the ’80s and ‘90s do not usually allow a simple preoperative or intraoperative setting. Often a full revision is needed. Nowadays, we consider mandatory the use of a modern modular knee or hip systems, in order to facilitate a future revision in case of failure: this is dramatic important particularly for younger patients. Nonetheless, in cases of severe joint destruction, there is a remarkable necessity to adapt the implant to the

altered anatomy of a joint with a failed prosthesis. The availability of wedges, stems, cones, offsets in the knee, or wedges, insert, necks, and heads in the hip represents an useful tool to face any bone defects or potential instability during surgery (Fig. **5**).

Fig. (5). Radiologic hystory of the case presented in Fig. (**2**). Primary TKA in a 42 years-old haemophilic patient with high-titre inhibitors **(a)** . Four years after TKA, aseptic loosening with mechanical failure of the femoral component and in the posterior aspect of the tibial baseplate induced by recurrent bleedings **(b)** . The availability of a modern modular knee system allowed the revision with the use of a "cone" in the femoral side to fulfil the severe bone loss, and a high constraint ensured a stability of the implant **(c)** . Radiographic aspect 4 years after revision **(d)** .

Fig. (6). Ceramic-on-PolyEthylene primary THA in a 41-years old subject affected by Haemophilia A with inhibitors **(a)** . Five years later, aseptic loosening with gross osteolysis in the acetabular and femoral components **(b)** . Revision with a trabecular metal cage, heterologous bone grafts enriched by autologous stem cells concentrate (white arrow), and a Metal-on-PolyEthylene coupling **(c)** . Postoperative x-rays at 6 months **(d)** and two years after surgery **(e)** with evidence of progressive osseointegration of bone grafts.

Often in revision THA and rarely in revision TKA bone loss management has to be planned. As for others type of patients, bone loss may easily be filled by bone grafts (autologous, homologous, synthetic) and various techniques (impaction grafting, engineered bone grafts by stem cells or Platelet Rich Plasma-PRP, bulky grafts) or in combination with modular parts of the implant (wedges, cones, inserts) [45 - 47] (Fig. **6**). However, very few reports in literature deal with these kind of approaches in Haemophilia.

In case of a septic failure, the setting may be more complex, in particular in patients with sinus tract, dehiscence, or skin alterations. The two-stage revision is to date considered the gold standard for the management of a failed infected implant. However, in case of large sinus tract or skin defect, a staged or simultaneous surgical step with skin coverage by a local or free flap may be necessary (Fig. **7**).

Fig. (7). Sinus tract in an infected knee implant of a haemophilic patient with inhibitors **(a)** . The first surgical step were the soft tissue debridement and dissection of the ipsilateral gemellus medialis **(b)** . Then the flap was isolated and rotated **(c)** and passed by a subcutaneous tunnel until reaching the loss of substance **(d)** . The final aspect of the flap after the positioning **(e)** .

Timing for the first of two stages and for the second stage is generally equivalent to non-haemophilic patients. The use of modern generation modular knee or hip systems is clearly convenient. Specifically, it is not uncommon the use of a "*megaprosthesis*", that consists in an implant indicated to substitute a large segment of a bone, in its epiphysis, metaphysis, and even its diaphysis (Fig. **8**) [48, 49]: its use is common in oncologic surgery, after large bone resections. Of noting, that this choice is technically demanding, needs a longer surgical timing, a larger dissection and tissues exposition, and finally it is correlated to mechanical complications more than standard primary and revision implants. Instability is more frequent for this kind of prostheses, particularly for hips, where an abduction

bracing is mandatory after surgery for several weeks. The use of megaprosthesis in knee surgery is generally easier than in the hip, but often correlated to limited range of motion of the joint and prolonged rehabilitation protocols.

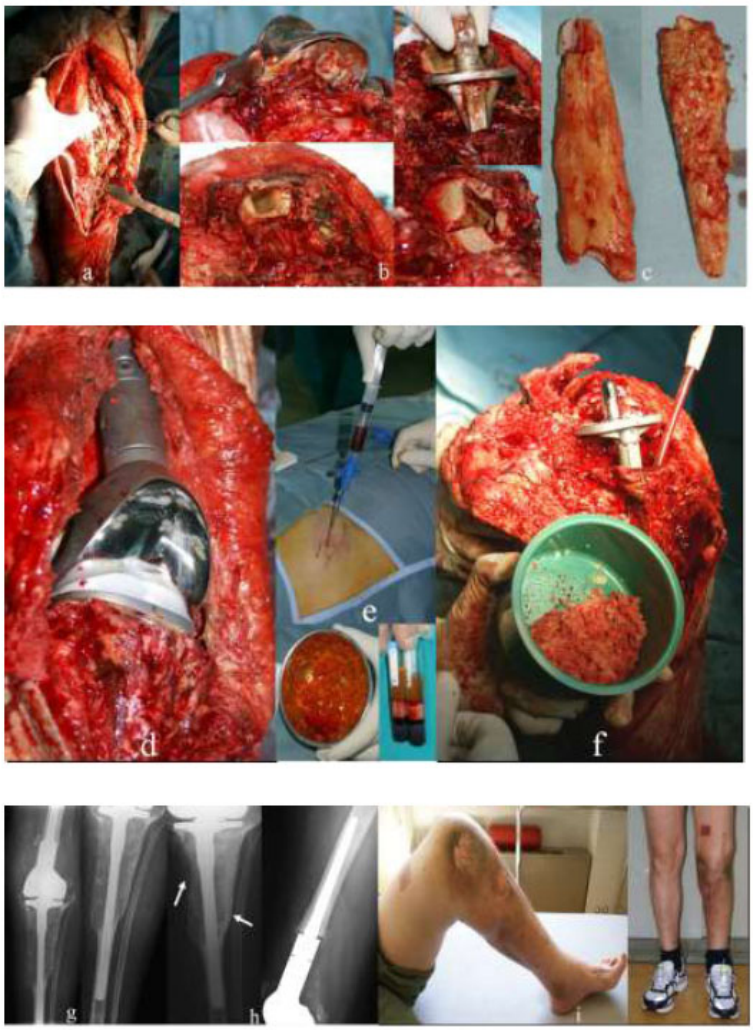

Fig. (8). Revision of a failed primary right TKA in a haemophilic patient with inhibitors **(a)** . Loose components **(b)** and cement removal **(c)** . Implant of a megaprostheses characterized by a cemented stem in the femoral side **(d)** , a cementless tibial component with long porous stem, and heterologous bone grafts enriched by autologous PRP and stem cells concentrate harvested by ipsilateral iliac crest (e and f). Radiologic follow-up at one month (g) and two years **(h)** . Of noting, the progressive enlargement of tibial corticals and resorption of heterologous bone grafts substituted by own bone (white arrows). Clinical aspect of the operated leg after 4 years **(i)** .

Finally, cases of failures and development of pseudotumours or aggressive acute septic failures are settings particularly challenging. In such cases, we should talk about "*salvage surgery*" more than "revision surgery". High rates of complications and expected not brilliant clinical outcomes are very common and patients and their relatives should be clearly informed. In our opinion, this kind of surgery when feasible should be reserved to young subjects as an attempt to avoid the other surgical approaches (joint fusion, amputation). In case of further failure, the option to face a more aggressive and "no-return" surgery is possible. On the other hand, we suggest a joint fusion or an amputation in adult or elderly haemophiliacs affected by this severe failure in order to quickly return to a more functional condition without facing further surgical procedures.

As mentioned in chapter 11, many haemophilic patients affected by severe knee arthropathy have been and in some cases still now are treated by primary TKAs with high constraint and cemented long-stemmed implants (Fig. **3a**) [29, 50 - 52].

This solution has been proposed in several cases to ensure a better postoperative stability and to dissipate all forces in the femoral and tibial diaphysis more than on the tibial insert. Typical indications have been represented by: severe tibial or femoral bone loss, excessive valgus or varus deformity, and noteworthy flexion contractures. However, most of these implants showed a very short survivorship with early loosening on the tibial baseplate and femoral component: wide zones of osteolysis and progressive radiolucencies have been reported with failure of the entire implants (Figs. **3b** and **4b**). At the time of revision, cement removal and bone defects represent the most challenging steps, particularly in young subjects (Figs. **8b** and **8c**). The typical setting in such cases is a gross bone loss and asymmetric flexion and extension gaps to be filled with modern modular revision implants and bone substitutes (Figs. **8e** and **8f**). Offsets for stems are crucial in order to restore an adequate balance between flexion and extension gaps, and to allow a recovery of the joint line close to the physiological (Fig. **9**) [53].

Tissue engineering techniques have recently gained interest in the field of reconstructive surgery also in Orthopaedics [45]. The management of large bone defects and the need to ensure the better osseointegration of metal components to bone has induced many surgeons to adopt autologous stem cell concentrations,

PRP combined with bone grafts or synthetic bioceramics to enhance the local metabolism of the host bone. The coupling of such these "*biological composites*" with modern high osteoinductive and osteoconductive implant surfaces seems to be very encouraging and efficient in the integration of metal components to the host bone (Figs. **8g** and **8h**) [46].

Fig. (9). Example of a modern revision knee implant. Oxidized zirconium femoral component is indicated in young subjects to ensure the lowest wear and the longest survivorship of the implant. Porous fluted stems are useful to allow a biological bone ingrowth. Finally, offsets are mandatory to adapt the implant to the peculiar anatomy of such these patients.

Rehabilitation after a revision surgery has to follow the basic principles of the management of a joint after multiple surgery but with the close collaboration between with dedicated figures as physical therapists, physiotherapists, orthopaedic surgeons, haematologists, and nurses. No protocols but tailored approaches have to be considered for each patients, as tailored is the haematological prophylaxis during rehabilitative pathways.

Joint fusion and amputation, once strongly considered as surgical options in severe cases, have nowadays lesser indications than before [50, 54]. However they still are indicated as the last attempt to save the limb after the failure of other surgical approaches (Fig. **10**). Joint fusion remains a discussed choice in the late stages of ankle arthropathy, being indicated mostly for adult or elderly subjects as an alternative for an ankle replacement when approaching an arthropathy [55]. It is mandatory after a failure of a previous ankle replacement given the good clinical outcomes even if resulting in a fixed joint [54]. Amputation followed by the wearing of an artificial prosthesis is today the indication for failures of any kind of medical and surgical procedures in patients with severe involvement of soft and hard tissues or in cases of failing multiple surgeries.

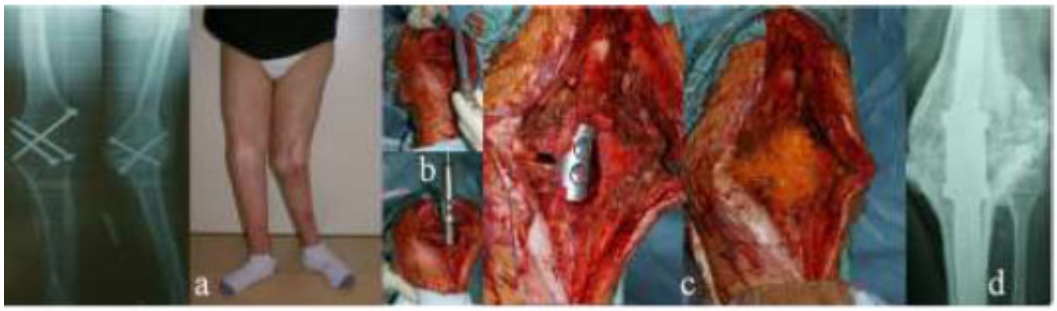

Fig. (10). Forty-eight years old haemophilic patient with an atraumatic mechanical failure of the fusion on his left knee performed 6 years before **(a)** . Intraoperative pictures showing the preparation for a new joint fusion by an cementless intramedullary nail and a biological composite (b and c). Radiologic follow-up at two years **(d)** .

The management of a failed THA or TKA implant in haemophilic subjects is clearly high demanding. The complexity lies not only in the preoperative multidisciplinary evaluation of a patient complaining a failed implant, but also in the medical expenses due to the haematological prophylaxis, the orthopaedic implant, and the costs for the hospital stay, usually prolonged with respect to standard revision settings. The prolonged hospitalization is in our opinion mandatory for a double purpose: it ensures the monitoring of critical patients, at risk for postoperative bleedings and infections; for the necessity of a long and often slow/soft rehabilitation, balancing a progressive functional recovery without exposing to further haemarthrosis a frail joint.

This requires the identification of specific facilities in which a multidisciplinary expertise may take care of this kind of patients and in which the opportunity to face such these costs is acceptable in an efficient manner and without uneconomical wastes.

CONCLUDING REMARKS

The management of a failed hip or knee implant is potentially complex in haemophilic patients. Several aspects have to be considered: the delicate haematological care and the related very high costs; the necessity of a modern modular implant, in order to adapt the prostheses to the patients and not vice versa; the several local settings of the patients that may be affect by an aseptic loosening, by a deep infection, and in some cases by a severe bone and soft tissue mortification; the need of a closed multidisciplinary monitoring and of a surveillance over the usually long rehabilitative care; and the consequent prolonged hospitalization.

Only specific facilities and specialized teams may be able to manage such these conditions.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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REFERENCES

[1] Sharkey PF, Hozack WJ, Rothman RH, Shastri S, Jacoby SM. Insall Award paper. Why are total knee arthroplasties failing today? Clin Orthop Relat Res 2002; (404): 7-13. [http://dx.doi.org/10.1097/00003086-200211000-00003] [PMID: 12439231]

[2] Fitzgerald SJ1, Trousdale RT. Why knees fail in 2011: patient, surgeon, or device? Orthopedics 2011; 9(34(9)): e513-5.

[3] Lombardi AV Jr, Berend KR, Adams JB. Why knee replacements fail in 2013: patient, surgeon, or implant? Bone Joint J 2014; 96-B(11) (Suppl. A): 101-4. [http://dx.doi.org/10.1302/0301-620X.96B11.34350] [PMID: 25381419]

[4] Sharkey PF, Lichstein PM, Shen C, Tokarski AT, Parvizi J. Why are total knee arthroplasties failing today--has anything changed after 10 years? J Arthroplasty 2014; 29(9): 1774-8.
[http://dx.doi.org/10.1016/j.arth.2013.07.024] [PMID: 25007726]

[5] Biemond JE, Venkatesan S, van Hellemondt GG. Survivorship of the cementless Spotorno femoral component in patients under 50 years of age at a mean follow-up of 18.4 years. Bone Joint J 2015; 97-B(2): 160-3.
[http://dx.doi.org/10.1302/0301-620X.97B2.34926] [PMID: 25628276]

[6] Carulli C, Villano M, Bucciarelli G, Martini C, Innocenti M. Painful knee arthroplasty: definition and overview. Clin Cases Miner Bone Metab 2011; 8(2): 23-5.
[PMID: 22461811]

[7] Solimeno LP, Perfetto OS, Pasta G, Santagostino E. Total joint replacement in patients with inhibitors. Haemophilia 2006; 12 (Suppl. 3): 113-6.
[http://dx.doi.org/10.1111/j.1365-2516.2006.01267.x] [PMID: 16684005]

[8] Sikkema T, Boerboom AL, Meijer K. A comparison between the complications and long-term outcome of hip and knee replacement therapy in patients with and without haemophilia; a controlled retrospective cohort study. Haemophilia 2011; 17(2): 300-3.
[http://dx.doi.org/10.1111/j.1365-2516.2010.02408.x] [PMID: 21070490]

[9] Rodriguez-Merchan EC. Total knee replacement in haemophilic arthropathy. J Bone Joint Surg Br 2007; 89(2): 186-8.
[http://dx.doi.org/10.1302/0301-620X.89B2.18682] [PMID: 17322432]

[10] Magone JB, Dennis DA, Weis LD. Total knee arthroplasty in chronic hemophilic arthropathy. Orthopedics 1986; 9(5): 653-7. [Short term].
[PMID: 3714579]

[11] Kelley SS, Lachiewicz PF, Gilbert MS, Bolander ME, Jankiewicz JJ. Hip arthroplasty in hemophilic arthropathy. J Bone Joint Surg Am 1995; 77(6): 828-34. [A>b].
[PMID: 7782355]

[12] Heeg M, Meyer K, Smid WM, Van Horn JR, Van der Meer J. Total knee and hip arthroplasty in haemophilic patients. Haemophilia 1998; 4(5): 747-51. [A>B].
[http://dx.doi.org/10.1046/j.1365-2516.1998.00183.x] [PMID: 9873881]

[13] Hicks JL, Ribbans WJ, Buzzard B, *et al.* Infected joint replacements in HIV-positive patients with haemophilia. J Bone Joint Surg Br 2001; 83(7): 1050-4.
[http://dx.doi.org/10.1302/0301-620X.83B7.11242] [PMID: 11603522]

[14] Park JJ, Slover JD, Stuchin SA. Recurrent hemarthrosis in a hemophilic patient after revision total knee arthroplasty. Orthopedics 2010; 11(33(10)): 771.

[15] Solimeno LP, Mancuso ME, Pasta G, Santagostino E, Perfetto S, Mannucci PM. Factors influencing the long-term outcome of primary total knee replacement in haemophiliacs: a review of 116 procedures at a single institution. Br J Haematol 2009; 145(2): 227-34.
[http://dx.doi.org/10.1111/j.1365-2141.2009.07613.x] [PMID: 19236610]

[16] Zingg PO, Fucentese SF, Lutz W, Brand B, Mamisch N, Koch PP. Haemophilic knee arthropathy: long-term outcome after total knee replacement. Knee Surg Sports Traumatol Arthrosc 2012; 20(12):

2465-70. [ahead of print].
[http://dx.doi.org/10.1007/s00167-012-1896-7] [PMID: 22293897]

[17] Duffy GP, Trousdale RT, Stuart MJ. Total knee arthroplasty in patients 55 years old or younger. 10- to 17-year results. Clin Orthop Relat Res 1998; (356): 22-7.
[http://dx.doi.org/10.1097/00003086-199811000-00005] [PMID: 9917663]

[18] Carulli C, Martini C, Matassi F. Primary Total Knee Arthroplasty in Haemophilia: a long-term experience with modern implants. Podium presentation at the 14th International Musculoskeletal Congress of Haemophilia. Belfast (UK). 2015.

[19] Wilde JT. HIV and HCV coinfection in haemophilia. Haemophilia 2004; 10(1): 1-8.
[http://dx.doi.org/10.1046/j.1351-8216.2003.00828.x] [PMID: 14962214]

[20] Mauser-Bunschoten EP, Bresters D, van Drimmelen AA, *et al.* Hepatitis C infection and viremia in Dutch hemophilia patients. J Med Virol 1995; 45(3): 241-6.
[http://dx.doi.org/10.1002/jmv.1890450302] [PMID: 7539831]

[21] Posthouwer D, Mauser-Bunschoten EP, Fischer K, Makris M. Treatment of chronic hepatitis C in patients with haemophilia: a review of the literature. Haemophilia 2006; 12(5): 473-8.
[http://dx.doi.org/10.1111/j.1365-2516.2006.01317.x] [PMID: 16919076]

[22] Brettler DB, Alter HJ, Dienstag JL, Forsberg AD, Levine PH. Prevalence of hepatitis C virus antibody in a cohort of hemophilia patients. Blood 1990; 76(1): 254-6.
[PMID: 2114186]

[23] Rodriguez-Merchan EC. HIV and HCV coinfected haemophilia patients: what are the best options of orthopaedic treatment? Haemophilia 2006; 12 (Suppl. 3): 90-101.
[http://dx.doi.org/10.1111/j.1365-2516.2006.01264.x] [PMID: 16684002]

[24] Ragni MV, Crossett LS, Herndon JH. Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts < or = 200/mm3. J Arthroplasty 1995; 10(6): 716-21.
[http://dx.doi.org/10.1016/S0883-5403(05)80065-8] [PMID: 8749751]

[25] Phillips AM, Sabin CA, Ribbans WJ, Lee CA. Orthopaedic surgery in hemophilic patients with human immunodeficiency virus. Clin Orthop Relat Res 1997; (343): 81-7.
[PMID: 9345211]

[26] Thomason HC III, Wilson FC, Lachiewicz PF, Kelley SS. Knee arthroplasty in hemophilic arthropathy. Clin Orthop Relat Res 1999; (360): 169-73.
[http://dx.doi.org/10.1097/00003086-199903000-00020] [PMID: 10101322]

[27] Rodriguez-Merchan EC, Wiedel JD. Total knee arthroplasty in HIV-positive haemophilic patients. Haemophilia 2002; 8(3): 387-92.
[http://dx.doi.org/10.1046/j.1365-2516.2002.00610.x] [PMID: 12010439]

[28] Ashrani AA, Key NS, Soucie JM, Duffy N, Forsyth A, Geraghty S. Septic arthritis in males with haemophilia. Haemophilia 2008; 14(3): 494-503.
[http://dx.doi.org/10.1111/j.1365-2516.2008.01662.x] [PMID: 18298584]

[29] Unger AS, Kessler CM, Lewis RJ. Total knee arthroplasty in human immunodeficiency virus-infected hemophiliacs. J Arthroplasty 1995; 10(4): 448-52.

[http://dx.doi.org/10.1016/S0883-5403(05)80144-5] [PMID: 8523002]

[30] Colvin R. Hemophilia and HIV standard of care. Common Factor 1997; 11(11): 10-1. [PMID: 11364844]

[31] Rodriguez-Merchan EC, De La Corte H. Orthopaedic surgery in haemophilic patients with inhibitors: a review of the literature In: Rodriguez-Merchan EC, Goddard NJ, Lee CA, Eds. Musculoskeletal aspect of Haemophilia. Blackwell Science Ltd 2000.

[32] Tagariello G, Iorio A, Santagostino E, *et al.* Italian Association Hemophilia Centre (AICE). Comparison of the rates of joint arthroplasty in patients with severe factor VIII and IX deficiency: an index of different clinical severity of the 2 coagulation disorders. Blood 2009; 23(114): 779-84. [http://dx.doi.org/10.1182/blood-2009-01-195313]

[33] Nagel K, Walker I, Decker K, Chan AK, Pai MK. Comparing bleed frequency and factor concentrate use between haemophilia A and B patients. Haemophilia 2011; 17(6): 872-4. [http://dx.doi.org/10.1111/j.1365-2516.2011.02506.x] [PMID: 21342368]

[34] Mannucci PM, Franchini M. Is haemophilia B less severe than haemophilia A? Haemophilia 2013; 1(19): 499-502.

[35] Ludlam C. Identifying and managing inhibitor patients requiring orthopaedic surgery - the multidisciplinary team approach. Haemophilia 2005; 11 (Suppl. 1): 7-10. [http://dx.doi.org/10.1111/j.1365-2516.2005.01152.x] [PMID: 16219043]

[36] Carcao M, Lambert T. Prophylaxis in haemophilia with inhibitors: update from international experience. Haemophilia 2010; 16 (Suppl. 2): 16-23. [http://dx.doi.org/10.1111/j.1365-2516.2009.02198.x] [PMID: 20132334]

[37] Aledort LM, Dimichele DM. Inhibitors occur more frequently in African-American and Latino haemophiliacs. Haemophilia 1998; 4(1): 68. [http://dx.doi.org/10.1046/j.1365-2516.1998.0146c.x] [PMID: 9873872]

[38] Leissinger C, Cooper DL, Solem CT. HTRS Investigators. Assessing the impact of age, race, ethnicity and inhibitor status on functional limitations of patients with severe and moderately severe haemophilia A. Haemophilia 2011; 17(6): 884-9. [http://dx.doi.org/10.1111/j.1365-2516.2011.02509.x] [PMID: 21447095]

[39] Carpenter SL, Michael Soucie J, Sterner S, Presley R. Hemophilia Treatment Center Network (HTCN) Investigators. Increased prevalence of inhibitors in Hispanic patients with severe haemophilia A enrolled in the Universal Data Collection database. Haemophilia 2012; 18(3): e260-5. [http://dx.doi.org/10.1111/j.1365-2516.2011.02739.x] [PMID: 22250850]

[40] Mancuso ME, Rumi MG, Aghemo A, *et al.* Hepatitis C virus/human immunodeficiency virus coinfection in hemophiliacs: high rates of sustained virologic response to pegylated interferon and ribavirin therapy. J Thromb Haemost 2009; 7(12): 1997-2005. [http://dx.doi.org/10.1111/j.1538-7836.2009.03624.x] [PMID: 19799716]

[41] Miles J, Rodríguez-Merchán EC, Goddard NJ. The impact of haemophilia on the success of total hip arthroplasty. Haemophilia 2008; 14(1): 81-4. [PMID: 18034823]

[42] Yoo MC, Cho YJ, Kim KI, Ramteke A, Chun YS. The outcome of cementless total hip arthroplasty in

haemophilic hip arthropathy. Haemophilia 2009; 15(3): 766-73.
[http://dx.doi.org/10.1111/j.1365-2516.2009.01986.x] [PMID: 19444974]

[43] Carulli C, Civinini R, Matassi F, Villano M, Innocenti M. The use of anti-osteoporosis drugs in total knee arthroplasty. Aging Clin Exp Res 2011; 23(2) (Suppl.): 38-9.
[PMID: 21970917]

[44] Massari L, Caruso G, Sollazzo V, Setti S. Pulsed electromagnetic fields and low intensity pulsed ultrasound in bone tissue. Clin Cases Miner Bone Metab 2009; 6(2): 149-54.
[PMID: 22461165]

[45] Carulli C, Matassi F, Civinini R, Innocenti M. Tissue engineering applications in the management of bone loss. Clin Cases Miner Bone Metab 2013; 10(1): 22-5.
[PMID: 23858306]

[46] Matassi F, Botti A, Sirleo L, Carulli C, Innocenti M. Porous metal for orthopedics implants. Clin Cases Miner Bone Metab 2013; 10(2): 111-5.
[PMID: 24133527]

[47] van Loon CJ, Wijers MM, de Waal Malefijt MC, Buma P, Veth RP. Femoral bone grafting in primary and revision total knee arthroplasty. Acta Orthop Belg 1999; 65(3): 357-63.
[PMID: 10546358]

[48] Stumpf UC, Eberhardt C, Kurth AA. Orthopaedic limb salvage with a mega prosthesis in a patient with haemophilia A and inhibitors - a case report. Haemophilia 2007; 13(4): 435-9.
[http://dx.doi.org/10.1111/j.1365-2516.2007.01476.x] [PMID: 17610563]

[49] Sunnassee Y, Wan R, Shen Y, Xu J, Southern EP, Zhang W. Preliminary results for the use of knee mega-endoprosthesis in the treatment of musculoskeletal complications of haemophilia. Haemophilia 2015; 21(2): 258-65.
[http://dx.doi.org/10.1111/hae.12541] [PMID: 25377302]

[50] Rana NA, Shapiro GR, Green D. Long-term follow-up of prosthetic joint replacement in hemophilia. Am J Hematol 1986; 23(4): 329-37.
[http://dx.doi.org/10.1002/ajh.2830230405] [PMID: 3788961]

[51] Kjaersgaard-Andersen P, Christiansen SE, Ingerslev J, Sneppen O. Total knee arthroplasty in classic hemophilia. Clin Orthop Relat Res 1990; (256): 137-46.
[PMID: 2114246]

[52] Legroux-Gérot I, Strouk G, Parquet A, Goodemand J, Gougeon F, Duquesnoy B. Total knee arthroplasty in hemophilic arthropathy. Joint Bone Spine 2003; 70(1): 22-32.
[http://dx.doi.org/10.1016/S1297-319X(02)00008-8] [PMID: 12639614]

[53] Innocenti M, Matassi F, Carulli C, Soderi S, Villano M, Civinini R. Joint line position in revision total knee arthroplasty: the role of posterior femoral off-set stems. Knee 2013; 20(6): 447-50.
[http://dx.doi.org/10.1016/j.knee.2013.05.012] [PMID: 23790671]

[54] Rodriguez-merchan EC, Goddard NJ. Chapter 10: Joint debridement, alignment osteotomy and arthrodesis. In: Rodriguez-Merchan EC, Goddard NJ, Lee CA, Eds. Musculoskeletal aspect of Haemophilia. Blackwell Science 2000.

[55] Daniels TR, Younger AS, Penner M, *et al.* Intermediate-term results of total ankle replacement and

ankle arthrodesis: a COFAS multicenter study. J Bone Joint Surg Am 2014; 96(2): 135-42. [http://dx.doi.org/10.2106/JBJS.L.01597] [PMID: 24430413]

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