Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis)

Short text

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Grade of recommendations

These recommendations are based on the results of available published medical studies, and graded accordingly according to modalities presented below (grade A, B, C). When no data was available, they were made on professional consensus (expert advice) within the work group. The absence of proof level does not mean that recommendations are not pertinent or useful.

Level of scientific proof according to literature	Grade of recommendations
Level 1 - High-power comparative randomized study - Meta-analysis of comparative randomized studies - Decision analysis based on adequately-performed studies	**A** Evidence based
Level 2 - Low-power comparative randomized study - Adequately -performed comparative non-randomized studies - Cohort studies	**B** Scientific presumption
Level 3 - Case-control studies **Level 4** - Comparatives studies with important bias - Retrospectives studies - Case series	**C** Weak level of proof

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Question 1: how should infections be classified?

1.1 Classification of prosthetic device bone and joint infections

1.1.1 Decisional items for the classification of prosthetic device bone and joint infections

It is recommended to classify bone and joint infections according to their etiology (mechanism of onset, type of prosthetic device, micro-organism), to the duration of evolution, to their localization, to their extension, and according to the terrain on which they occur.

1.1.1.1 Definition of the type of prosthetic device used in orthopedic surgery and infectious risk

1.1.1.1.1 Osteosynthesis devices

Internal devices: they may be placed on the bone or in centromedullary position. At the rachis level, they can be rods, screw, grafts, inter-somatic cages, or artificial ligaments the removal of which is often impossible or must be delayed.

External fixators: the cutaneous outlet of pins is constantly colonized by skin flora.

1.1.1.1.2 Prostheses

This type of device is considered as definitive. It cannot be removed without an important functional degradation.

1.1.1.1.3 Bone substitutes and donor grafts

Curing the infection on bone substitute is almost always done by removing it.

1.1.1.2 Length of bone and joint infection evolution

The only consensual point in the literature is that the therapeutic result depends on the length of infection evolution. The longer the infection evolves, the more difficult it is to cure.

Bone infection is commonly defined as acute or chronic.

These terms do not have the same meaning for everybody. *For the clinician*, an acute infection presents as local or general inflammatory signs and/or recent pain, and a chronic infection is more one with suggestive radiological signs; *for the microbiologist*, it is the biofilm (dynamic entity made of a polysaccharidic substance secreted by bacteria called «slime» allowing for the definitive adherence of bacteria on prosthetic devices), and the polymorphism of isolated colonies in deep samplings which define chronicity; *for the surgeon*, an acute infection is one which could be cured without removing the prosthetic device.

The terms «acute or chronic» should not be mistaken for the delay before diagnosis of infection after surgical placement of the prosthetic device.

Finally, hematogenous infection, presenting as an acute infection, may occur early or late (after a symptom-free period) after surgery (Cf. figure 1 bis).

It is recommended classify an infection as early when occurring during the first post-operative month, as delayed when occurring between the second and sixth post-operative months, and as late when occurring after the sixth post-operative month.

1.1.1.3 Mode of bacterial contamination

1.1.1.3.1 Direct inner contamination

Due to an invasive procedure

These are infections occurring after a therapeutic or diagnostic procedure and infections of the surgical site.

Post-traumatic

Skin effraction may be caused by a wounding instrument, or by another mechanism (open fracture, pressure wounds, vascularitis, arteritis, etc). The bone and prosthetic device are exposed to the air.

1.1.1.3.2 "Hematogenous" contamination

Joint prostheses

A hematogenous infection on a joint prosthesis will cause septic arthritis at first. This explains that cure may be achieved without removing the prosthesis if the time lapse before management is short. Second, the prosthetic device itself and then the bone-cement interface are contaminated.

Other orthopedic devices

Any inserted orthopedic device may be colonized hematogenously.

1.1.1.3.3 Contamination by contiguity

The soft tissue infection may spread to nearby osteo-articular structures by preferentially following lymphatic drainage territories.

1.1.2 What are the current classifications?

There are several classifications without consensus on their use. It is recommended to analyze 7 fundamental points:

- suspected mode of contamination (direct, hematogenous, by contiguity)
- symptom-free period, allowing to make the difference between post-operative infection and hematogenous infection: figures 1 and 1 bis
- infectious state (identified pathogens, severity of infection impact)
- mechanical state of the infected site (prosthesis loosened or not, fracture consolidated or not, presence of prosthetic device or not, removable or not);
- localization of the infection (peripheral bone, joint, rachis);

- state of skin and soft tissues;

- state of the patient (functional and general, immune status, underlying terrain, and environment context)

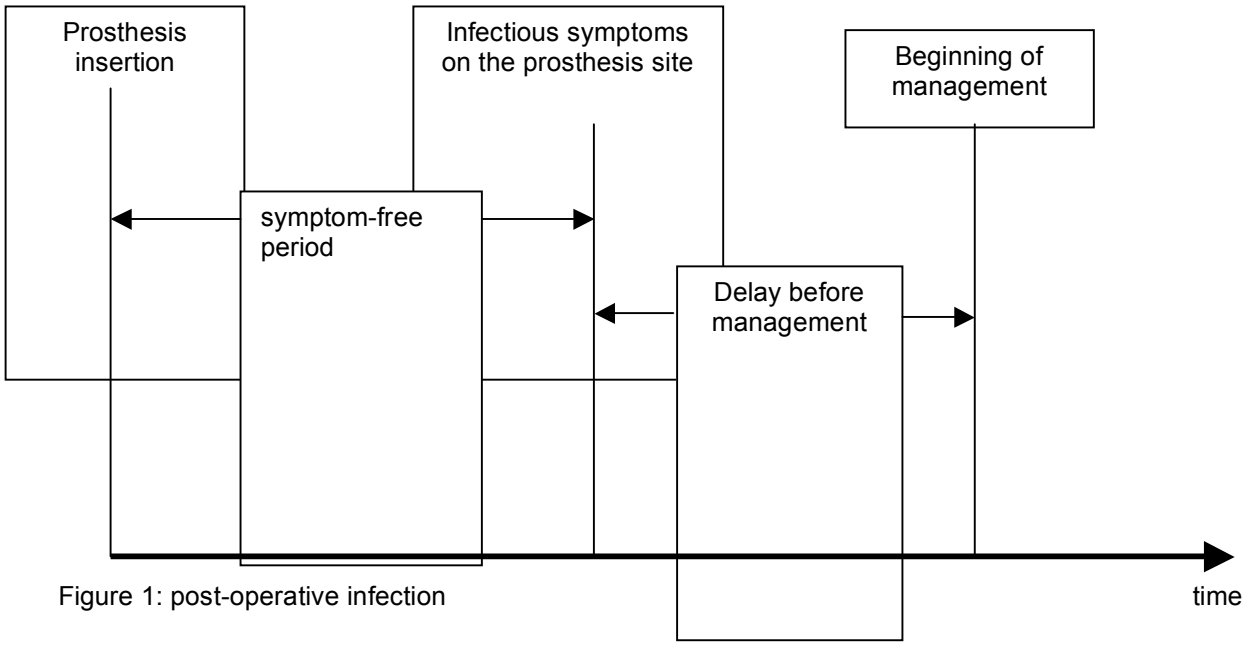

Figure 1: post-operative infection

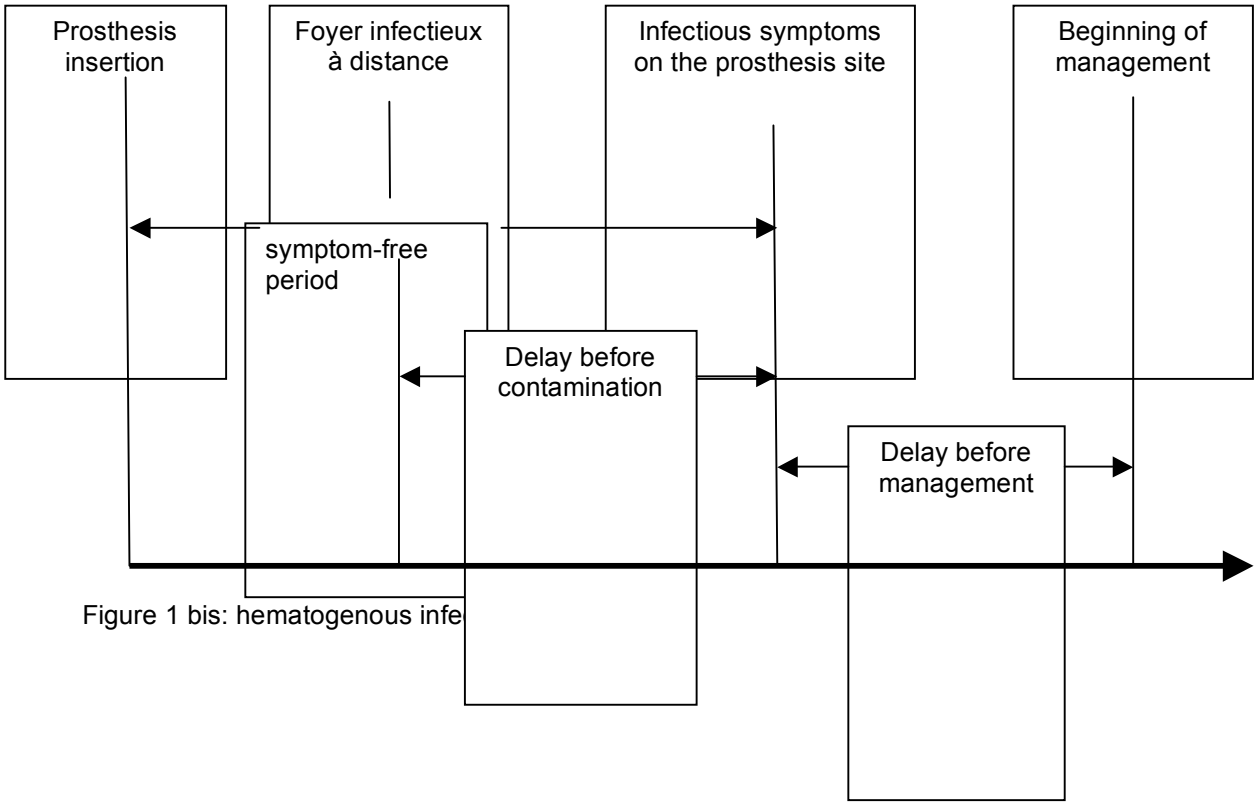

Figure 1 bis: hematogenous infe

1.2 What are the risk factors (terrain, immunodepression, vascular diseases, irradiation)?

The rate of infection is weak today in orthopedic and traumatological surgery. It is 0.5% for the best-recorded results in hip prosthetic surgery, and ranges between 3-4 to 5-7% for traumatological surgery. Given these weak rates, determining risk factors for the patient is difficult.

For open fractures, only a tibial localization and the severity of soft tissue lesions assessed with the Gustilo classification (addendum 1) appear as significant risk factors of surgical site infection (SSI) (**level 2**).

For closed fractures of long bones, there is no evaluation of infectious risk factors. Diabetes clearly appears as a factor for difficult healing after osteosynthesis of the ankle or foot, directly exposing to SSI (especially when there is an associated arterial disease and/or neuropathy) (**level 2**).

In orthopedic surgery, there is a significant increase of SSI risk for several factors: patient more than 65 years of age (**level 2**), presence of another infectious site in the patient (**level 2**), pre-operative hospital stay above 4 days in the 6 weeks before surgery (**level 2**). There is a weak increase of the risk in case of obesity, corticotherapy, tobacco abuse, recent radiotherapy on the operative site, difficult healing, pressure wound close to the operative site, hematoma (**level 2**), and for rheumatoid polyarthritis **(expert advice).**

For rachis orthopedic surgery, diabetes on one part, increased peri-operative glycemia on another other part, appear as infectious risk factors in some case-control studies, with a weak level of proof **(level 3)**.

It is not recommended to interrupt corticotherapy during the peri-operative period for rheumatoid polyarthritis, because of the risk for acute suprarenal insufficiency. Maintaining the treatment with methotrexate does not increase the risk for SSI (**level 1**). In one study, leflunomide was reported to increase the risk of healing incident compared to patients treated with methotrexate (**level 1**); but the infectious risk was not evaluated.

Data is still lacking concerning maintenance or interruption of anti-TNF (etanercept, infliximab, adalimumab), because of several contradictory studies. Nevertheless, in agreement with HAS recommendations, it is strongly advised to stop anti-TNF from 2 to 5 half lives before surgery and until skin healing is complete. It is also necessary to stop anti-TNF as soon as the diagnosis of prosthetic device infection is made.

1.3 Is there any available epidemiological data in France for prosthetic device bone and joint infections?

Surveillance of SSI is a national priority in the fight against nosocomial infections thanks to data from clinical studies and surveillance data from the RAISIN network (Alert, Investigation, and Surveillance of Nosocomial Infections).

1.3.1 French epidemiology of prosthetic device bone and joint infections.

1.3.1.1 Epidemiology of infections on joint prostheses

The data collected from 1999 to 2005 form the RAISIN database is summarized in table I. The comparison of incidences for total hip prosthesis (THP) and total knee prosthesis (TKP) does not indicate any significant linear tendency. The major drawback of this surveillance data is that the post-operative follow-up of patients was limited to a maximum of 30 days.
A synthesis of the 6 French incidence studies is presented in table II. Each study is briefly described.

1.3.1.2 Epidemiology of infections on joint material (prostheses excluded)

According to the RAISIN database, the incidence of infections on osteosynthesis material was
1% (out of 63,839 surgeries), and ranged from 0.5% for surgeries with an NNISS score (National Nosocomial Infection Surveillance Score) = 0 to 3.7% for surgeries with an NNISS score >1.

1.3.2 Microbiology of prosthetic device infections in orthopedic surgery

The microbiological data of the main French studies on prosthetic device infections is presented in table II. Staphylococci are the most frequently isolated bacteria. The frequency of coagulase negative staphylococcal strains (especially *Staphylococcus epidermidis*) the same as that of *Staphylococcus aureus* (**expert advice**). The infections are monomicrobial most of the time (90%).
The other isolated bacteria include streptococci (beta-hemolytic or not hemolytic), enterococci, *Pseudomonas aeruginosa*, enterobacteria (*Escherichia coli*, *Enterobacter cloacae*, *Proteus mirabilis, Bacillus cereus*), and anaerobic (*Propionibacterium acnes*). It should be stressed that in the presence of prosthetic device, any bacterial strain may be implicated, including *Brucella*, *Pasteurella*, *Listeria*, *Haemophilus*, *Campylobacter*, etc. Some bacteria can only be identified with molecular biology techniques (*Mycoplasma, Trophyrema whippleii*). Finally, fungal infection is also possible.

1.3.3 Discussion

In the absence of an inter-hospital registry, every institution should be able to implement its own surveillance with a methodology adapted to its objectives and capacity. In the future, a surveillance system based on the Scandinavian model could be proposed: the creation of a national registry.

Table I – Incidence of SSI on joint prostheses. National RAISIN data (1999-2005) [29].

Types of surgery	Incidence for surgeries with an NNISS score = 0	Incidence for surgeries with an NNISS score = 1	Incidence for surgeries with an NNISS score > 1 (2 or 3)	Global incidence
Total hip prosthesis (THP)	0.7%	1.2%	2.6%	0.9%
Hip joint prosthesis (except for THP)	1.1%	2.2%	2.9%	1.6%
Knee joint prosthesis	0.4%	0.6%	2.3%	0.6%
Other joint prostheses	0.7%	1.5%	1.4%	1.0%

Table II – Main French studies (non RAISIN) on the incidence of SSI on joint prostheses.

Studies	Types of studies	Number of surgeries	Types of surgeries	Definition of infection	Microbiology	Length of post-operative follow-up	Incidence
Dumaine et al. 2007 [30]	Prospective, monocentric	2,646	Joint prostheses (hip and knee)	2 positive deep samplings + clinical and biochemical data (CRP)	*S. aureus* : 58% MRSA: 10% Monomicrobial in 70% of cases	12 months	0.9%
Debarge et al. 2007 [31]	Retrospective, monocentric	923	TKP in first intention	Isolation of bacteria on at least one deep sampling performed before re-intervention for a suspected infection	*S. aureus* ≈ 90% Monomicrobial in 100% of cases	12 à 123 months	2.1%
Lecuire et al. 2003 [32]	Prospective, monocentric	3,821	THP: 2,745 TKP: 1,076	clinical and biochemical criteria of CDC. Absence of complementary microbiological criteria	*S. aureus* ≈ 50 % Monomicrobial in 75% of cases	unknown	THP: 0.55% TKP:1.67%
Eveillard et al. 2001 [20]	Prospective, monocentric	790	PTH	Deep infections. Bacteria isolated on a deep sampling during re-operation for a suspected infection .	Majority of MRSA	From 1 month to 4 years. 80% of patients followed-up at 12 months	1.11%
Eveillard et al. 2003 [33]	Prospective, monocentric	210	PTG				4.29%
Merrer et al. 2007 [34]	Prospective, multicentric	396	Hemiarthroplasty for For femur neck fracture	Deep and superficial infections	Majority of MRSA	12 months	6.9%

THP: total hip prosthesis; TKP : total knee prosthesis. MRSA: methicillin resistant *Staphylococcus aureus*

Question 2: how can the diagnosis of prosthetic device bone and joint infection be proved?

2.1 What are the clinical signs suggesting a prosthetic device bone and joint infection in a patient with a joint prosthesis?

The presence of a fistula close to the prosthesis proves the infection until contradictory evidence is established **(level 3).**

In the months following the insertion of a joint prosthesis, the following clinical signs are suggestive of prosthesis infection **(level 3)**:

- unusually strong pain or its recurrence after a symptom-free period;
- purulent discharge of the surgical wound;
- disunion, or necrosis, or scar inflammation.

The presence of general signs (fever, shivering) increases the probability of an infection.

After insertion of a joint prosthesis, it is recommended to suggest the presence of infection in case of pain and/or the presence of a radiologically proven loosening, especially if the prosthesis was inserted recently **(grade C).**

In case of a long free interval between insertion of prosthesis and the onset of infectious signs close to the prosthesis, it is recommended to look for a remote infectious focus (“hematogenous” infection) **(grade B).**

In a patient with a joint prosthesis or osteosynthesis material, in case of sepsis (addendum 2) and in the absence of another infectious sign after a clinical examination, an infection of the osteosynthesis material will have to be considered.

The absence of clinical local and general inflammatory signs does not allow to rule out a prosthesis infection **(level 2).**

2.2 What are the biological criteria suggesting a prosthetic device bone and joint infection and what is their diagnostic value?

No biological parameter is by itself specific of a prosthesis infection.

Blood leucocytosis does not have a good positive and negative predictive value in case of a prosthesis infection **(level 2).**

A normal value of SR and/or CRP does not rule out a prosthetic device bone and joint infection **expert advice**).

In the months following implantation of bone and joint material, it is recommended to monitor the evolution curve of C-reactive protein (CRP) serum level (and not its absolute value), which is correlated to an infection. It is recommended not to measure the sedimentation rate (SR) which has no diagnostic value **(grade C).**

3 months after the insertion of a prosthesis, and if it is suspected to be infected, it is recommended to measure SR and CRP **(grade B).** Interpreting the results must be made in the absence of confounding factors (infection of an other origin, inflammatory rheumatism flare, etc.), according to the patient's age, and according to the renal function for the SR. The minimal thresholds beyond which an infection is suspected, varies between 22 and 30 mm for the SR, and between 10 and 13.5 mg/l for the CRP.

2.3 What is the contribution of imaging (radiology, ultrasonography (US), tomography, MRI, nuclear imaging)?

2.3.1 What are the radiological signs suggesting a prosthetic device bone and joint infection?

It is strongly recommended to perform standard X ray even if 50% remain normal and if there are no formal radiological signs of prosthetic infection **(grade B).** The radiological signs to screen for are the following **(level 2)** :

- presence of a sequestrum, small and very dense bone fragment;
- A clear and extended lucent line around the material the width of which increases by more than 2 mm over a period of one year;
- zones of unclear osteolysis;
- extensive circumferential periosteal reaction;
- presence of intra-articular gas;
- mobilization or fracture of the osteosynthesis material.

The sensitivity of radiography is 14% and its specificity is 70%.

2.3.2 What tomographic imaging suggests a prosthetic device bone and joint infection?

It is recommended to perform a scanner with an IV injection of an iodine contrast medium, the best examination, in the presence of osteosynthesis material, to assess the bone structure on peripheral bone **(grade B)**. It also allows to analyze soft tissues. It may be artifacted by osteosynthesis material.
The tomographic images of a prosthesis infection are the following **(level 2)** :

- presence of periosteal appositions;
- unclear osteolysis around the material;
- soft tissue abnormality;
- fluid collection in soft tissues.

If a joint infection is suspected, the absence of intra-articular effusion has a negative predictive value of 96%.

2.3.3 What are the US signs suggesting a prosthetic device bone and joint infection?

Ultrasonography allows to screen for fluid collection, intra-articular effusion or effusion localized at the level of a serous bursae, thickening of soft tissues and hyperemia revealed by Doppler ultra-sound **(level 2)**. If joint infection is suspected the absence of intra-articular effusion has a strong negative predictive value.

2.3.4 What MRI imaging suggests a prosthetic device bone and joint infection?

MRI allows to visualize with precision abnormalities of soft tissues in case of infection on osteosynthesis material. The bone structure in contact with osteosynthesis material cannot be analyzed and there are abnormal signals from the medullar bone in the early post-operative period. It is recommended to perform sequences allowing to decrease artifacts due to the material (fast spin-echo). It is recommended to make an intravenous Gadolinium® injection.

Radiological signs suggesting infection around the osteosynthesis material are **(level 2)**:

- inflammatory soft tissue edema in T2 hyper signal increasing after Gadolinium® injection;
- intra-osseous or soft tissue fluid collection with annular enhancement during Gadolinium® injection (the central zone is not enhanced);
- fistula in T2 hyper signal enhanced after Gadolinium® injection;
- intra-articular effusion or serous bursae effusion in T2 hyper signal without contrast enhancement after Gadolinium® injection;
- bone sequestration appearing as hypo signal on all sequences.

MRI has a good diagnostic value in case of rachis infection. MRI screening for contrast enhancement of the discal and epidural space with central avascular necrosis will be performed when used in association with the previously described signs.

2.3.5 What are the arthrographic signs suggesting a prosthetic device bone and joint infection?

If arthrography does not allow to confirm the diagnosis of bone and joint infection on material, it is indicated to check for extension of infection in the pre-operative period.
Arthrography allows to visualize a fistula path and/or a para-articular fluid collection and to perform a puncture for bacteriological analysis before opacification **(level 2)**.
This test should not be performed for follow-up of infection on material.

2.3.6 What tests should be done in case of fluid collection?

Collection puncture next to osteosynthesis material or in a prosthetic joint is mandatory and must be performed in strict surgical asepsis. If it is difficult to perform, it can be done under scope control or during ultrasonography, tomography, or arthrography **(grade B).** The sensitivity of this diagnostic method varies according to studies (between 77 an 97%).
It is recommended only in case of clinical suspicion of material infection and must be performed some time after any antibiotherapy **(grade C).**

2.3.7 What nuclear medicine tests should be performed and what are the scintigraphy signs in case of a prosthetic device bone and joint infection?

A bone scintigraphy can be performed with Hydroxy-Diphosphonate tagged with Technetium 99 (HDP-Tc99m) or with Hydroxy-Methyl-Diphosphonate tagged with Technetium 99 (HMDP-Tc99m) which will reveal osteoblastic activity (with 3 successive stages: vascular, tissular, and osseous later). In case of infection, this test which is positive early, will demonstrate abnormal fixation in the 3 stages **(level 2).** Its sensitivity is 90 to 100% but its specificity is only 30 to 40%. Its negative predictive value is close to 100%.
The abnormal result of bone scintigraphy with HDP-Tc99m or with HMDP-Tc99m is not specific of infection. Indeed, after insertion of a prosthesis or synthesis material, an abnormal fixation may persist ranging from, according to studies, between 6 and 12 months for the hip and up to 24 months for the knee.
In this case, it is strongly recommended to associate scintigraphy with PMN tagged with Hexa-Methyl-Propylene-Amine-Oxim tagged with Technetium 99 (HMPAO-Tc-99m) with late images 24 hours after reinjection of PNMs. If there is an infection, this test will show an abnormal fixation which should persist on images made 24 hours after injection. If imaging positive at 24 h, it is possible to improve the localization of the infectious focus with a helicoidal scan and single photon emission computed tomography (SPECT) if the test is available. This scintigraphy has a sensitivity of 81 to 97% and a specificity of 89 to 100% **(level**

2). A delay of at least 6 months between prosthesis insertion and scintigraphy is necessary for its interpretation.

If *in vitro* tagging of autologous leucocytes is not possible, scintigraphy with anti-granulocytes antibodies (i.e. Leukoscan®) may be performed.

In some cases, it is possible to perform a medullar scintigraphy (sulfo-colloids tagged with Technetium 99) if there is suspicion of medullar remodeling following surgery. In this case, the absence of congruence between the two types of radiopharmaceutical imaging strongly suggests sepsis.

If rachis infection on osteosynthesis material is suspected, it is possible to perform scintigraphy with Gallium 67 (images made 48 to 72 hours after injection of the radiopharmaceutical agents). When associated to Tc99m-HMDP bone scintigraphy, this test has a diagnostic specificity of 75 to 91 % **(level 2).**

18 FDG SPECT has no indication for the diagnosis of infection of bone and joint prosthesis or for infection on rachis material.

2.3.8 What imaging strategy should be chosen in case of a prosthetic device bone and joint infection?

In case of early (within the 1st month following the insertion of osteosynthesis material) **or hematogenous infection**, the contribution of imaging is limited. In case of fluid collection in contact with osteosynthesis material difficult to puncture, it is recommended to perform the puncture under US guidance and respecting surgical asepsis conditions **(grade C).** If there is suspicion of early infection on rachis material, MRI is advised.

In case of delayed infection (occurring between the 2nd and the 6th month) **or late** (after the 6th month), it is recommended to perform standard first intention radiography because of its simplicity, its low cost, and its reproducibility **(grade B)**.

In second intention, it is recommended to perform a CT scan with iodine contrast injection **(grade B)**. In case of fluid collection in contact with osteosynthesis material difficult to puncture, it is recommended to perform the puncture under scope, US, tomography, or arthrotomographic guidance respecting surgical asepsis conditions **(grade C)**.

In third intention (non-informative radiography, absence of collection, or negative puncture), imaging with radioisotopes (bone scintigraphy associated to scintigraphy with tagged PNM) is recommended, under the condition that they are performed in the conditions defined in the previous paragraph **(grade B)**.

If infection on rachis osteosynthesis material is suspected, MRI wit Gadolinium® injection and bone scintigraphy associated to scintigraphy with Gallium are the most efficient tests.

2.4 What is the contribution of microbiology and anatomopathology?

2.4.1 How should diagnostic microbiological sampling be performed?

It is recommended to wait a minimum of 15 days after any antibiotherapy before any test, so as to decrease the rate of false negative samples (except in case of sepsis and after evaluating the risk for disseminated infection) **(expert advice)**.
It is recommended to perform pre-operative sampling with surgical asepsis (puncture of a joint or of a fluid collection in contact with osteosynthesis material) when there is a diagnostic doubt of bone and joint infection. In case of positive result, this allows to plan surgical management (surgery in 1 or 2 steps: Cf 3.2.1.2.3) and to adapt antibiotherapy in the post-operative period. A negative result does not rule out a diagnosis of infection.
In case of fever and other aspecific clinical signs, it is recommended to perform hemocultures with enough blood vials for aerobic and anaerobic bacteria and to perform pre-operative sampling (puncture of a joint or of an abscess next to material respecting surgical asepsis conditions) so as to be able to rapidly initiate probabilistic antibiotherapy before considering surgery ASAP.
It is strongly recommended to perform sampling again during surgery.
It is recommended to respect surgical asepsis when performing the sampling so as to prevent false positive samples **(expert advice)**.

2.4.1.1 Pre-operative sampling

It is strongly recommended not to sample with a swab on the scar, even if it is not healed.
It is not recommended to perform sampling from the outlet of a fistula.
It is recommended to perform a puncture (radio guided eventually) in case of intra-articular effusion or abscess in contact with osteo-articular material (respecting surgical asepsis conditions).
It is recommended to keep the sampled fluid in the sampling syringe. It is also recommended to inoculate hemoculture vials for aerobes and anaerobes if the delay for transportation to the lab is superior to 2 hours, and a part of the fluid must be collected in a heparinized tube heparin for direct examination: cytology and staining.
If there is only granulomatous tissue without fluid collection, it is possible to perform a True-cut biopsy **(grade B)**.
In case of rachis infection, it is recommended to perform percutaneous biopsies (Cf chapter 3.2.4) which should not delay surgical management.

2.4.1.2 Per-operative sampling

It is recommended to sample at the beginning of surgery, without any antibiotherapy, and before any antibioprophylaxis.
It is strongly recommended not to sample with swabs.
It is recommended to perform 5 samplings at the level of macroscopically pathological areas **(grade B)**. These samplings may be liquid (pus, articular fluid) or solid (granulomatous tissue, bone tissue,

interposition tissue, and any suspicious tissue). The localization of each sampling site must be documented.
It is recommended to change sampling tool between each sampled site.
It is strongly recommended to rapidly send samples to the laboratory in sterile vials, in less than 2 hours (Cf 2.4.2).

2.4.1.3 Post-operative samplings

In case of septic surgery, the positivity (with the same bacterium or another) of cultured drain fluids (sent to the bacteriological laboratory after 72 hours at the latest) seems to be linked with a higher risk of infection relapse or recurrence **(level 2).**
In case of infection on external fixator pin, it is recommended to perform sampling along the pin (Cf chapter 3.2.6).

2.4.2. How should microbiological samples be carried to the laboratory?

If the time for transport is superior to 2 hours, it is recommended to store samples in transport medium (especially for the survival of anaerobes). Transport must be made at ambient temperature. It is recommended that the laboratory records delay in transport of samples.
It is strongly recommended that samples be adequately labeled for identification (last name, first name, and sites of sampling) and be sent along with a specific order form. Screening for possible mycobacteria must be specified on the order form.

2.4.3. What microbiological techniques should be implemented for the diagnosis and interpretation of samples?

All the samplings must be handled with a specific technique under a laminar airflow hood type PSM2 with single use protective wear (changed once a day) and sterile gloves (changed regularly) to prevent external contamination as much as possible. It is recommended to use single use material and agar as fresh as possible.

2.4.3.1 Pre-operative samplings: articular fluid

It is recommended to perform a cytological test (count and formula) in the 2 hours following sampling. More than 1,700 leucocytes/mm^3 (sensitivity 94% and specificity of 88%) and more than 65% of PMN neutrophils are strongly suggestive of infection on prosthesis in articular fluid **(level 2)**. Direct bacteriological examination after Gram staining of a cytocentrifugation pellet may allow to visualize bacteria.
It is recommended to seed the articular fluid on enriched agars to be incubated in aerobic condition, under 5% of CO2 and in anaerobic condition, and to inoculate hemoculture vials for aerobics and anaerobes.
It is recommended to maintain incubation of culture media for at least 14 days **(expert advice)**. It is recommended to seed enriching broths again at the end of incubation even if they are not cloudy.

2.4.3.2 Per-operative samplings

It is recommended to crush solid samples (bone or tissue fragments) so as to free bacteria from biofilm. It is recommended to seed liquid and crushed samples on solid and liquid enriched media and eventually on a medium for mycobacteria on the clinician's request.

It is recommended to perform direct examination of crushed sample smear to screen for PMN neutrophils (better identified after May Grunwald staining) and bacteria (Gram staining). The sensitivity of direct bacteriological examination is weak (6%) whereas the specificity is close to 100%.

It is recommended to freeze a part of samples to -80 °C for specific screening (mycobacterium, fungus) and eventually for molecular biological techniques.

It is recommended to maintain incubation of solid culture media (for 5 days in aerobic conditions and for 8 days in anaerobic conditions) and liquid culture media (for 14 days) to allow isolation of slow growth bacterial micro colonies called «small colony variants », *Propionibacterium acnes* and bacteria of different species which appear on agarose later (pluri-microbial samples). It is recommended to seed enriching broths again systematically at the end of incubation even if they are not cloudy.

It is recommended to identify all the different colonies, especially staphylococci

It is recommended to perform an antibiogram on the various types of colonies isolated. It is necessary to asses glycopeptide MICs on staphylococci according to the recommendations of the S.F.M. Antibiogram committee and to check, if possible, the susceptibility to oxacillin by screening for the *mecA* gene. It is necessary to assess MICs of beta-lactams on the non-groupable streptococci.

2.4.4 What is the contribution of anatomopathological examination for the diagnosis of prosthetic device bone and joint infections?

It is recommended in every case to perform an anatomopathological examination of bone tissue and synovial fluid. It is recommended to define a prosthetic infection histologically according to the presence of more than 5 PMN neutrophils per high magnification field (x 400) in at least 5 different microscopic fields on bone sample. In this case, the sensitivity and specificity of the examination will range respectively from 43 to 100% and from 81 to 98%.

Finally, the contribution of the histological examination is to suggest a diagnosis of mycobacterial or fungal infection.

2.5 What data suggests the diagnosis (proved infection, and non detectable or no infection)?

There is no published consensus on the criteria allowing to define a bone and joint prosthetic infection. The criteria correspond to a panel of arguments among which microbiology is predominant. The work group, with an exploratory objective, has judged useful to propose a binary classification (proved infection /infection probably excluded or not detectable) by considering that between the two, there are several situations of possible infection for which specific criteria cannot be defined. Finally, in this chapter, we

consider that the initial clinical, biological, and/or imaging approach, has allowed to suspect infection. We consider that 5 samplings at least were performed every time.

2.5.1 Proved infection

- Presence of a fistula in contact with the prosthesis or the implant **(level 3),**
- presence of pus in the joint or in contact with the prosthesis or the implant **(expert advice)**,
- presence of at least 3 samples (3 per-operative samples or 2 per-operative samples + 1 sample per joint puncture performed a few days before surgery) positive for the same bacterium(a) belonging to the skin flora (ex: coagulase negative staphylococcus, *Propionibacterium acnes,* corynebacterium, etc.) and the isolation of which raises the question of a possible contamination **(level 2)**,
- presence of at least 1 positive sample (1 sample per joint puncture or 1 per-operative or hemoculture sample) for a bacterium not belonging to the skin flora and for which the question of a possible contamination is not raised (ex: *Staphylococcus aureus*, enterobacteria, *Pseudomonas aeruginosa*, etc.) or for a bacterium exceptionally isolated for which the question of a possible contamination is not raised (ex: *Streptococcus pneumoniae, Salmonella, Listeria, Campylobacter, Pasteurella*) **(expert advice)**.

2.5.2 Infection probably excluded or not detectable

An infection is considered as probably excluded or not detectable in the absence of a fistula or pus in the joint or in contact with the implant if one of the following criteria is met:

- All the are sterile (under the condition that they were sampled after 15 days without any antibiotherapy) and when there is no histological sign of infection **(level 2)**,
- Only 1 per-operative sample is positive for a skin flora pathogen (coagulase negative staphylococcus, *Propionibacterium acnes*, corynebacterium, etc.) without histological sign of infection and with less than 65% of PMN neutrophils in the articular puncture fluid **(level 2)**.
- In these 2 situations, CRP < 10 mg/l may support the absence of infection**.**

<u>Question 3</u>: what are the modalities of therapeutic management?

3.1 What is the rational for the therapeutic strategy?

The scientific rational based on experimental *in vitro* or animal studies does not allow a gradation as suggested.

3.1.1 Biofilm and biomaterials

In vitro studies have proven that the metallic surface of a prosthesis or osteosynthesis material is not inert. The oxides contained in the material are responsible for a secondary binding interaction surface for bacteria.

A bacterial inoculum below 1,000 forming colonies is considered as sufficient to trigger the infectious process.

This process begins by a phenomenon of attraction-adhesion during which bacteria are reversibly adsorbed on the material. Then, the bacteria irreversibly colonize the material. From then on, bacteria develop a survival strategy within a dynamic entity defined as the biofilm, made of a polysaccharidic substance secreted by bacteria called « slime » which permits the definitive adherence of bacteria on the material.

The bacteria in the biofilm are organized in micro-colonies (« small colony variant ») under the influence of inter-cellular communications leading to a stationary growth phase due to the absence of ATP production. This has for consequence:

- to limit the activity of some antibiotics which diffuse badly in the biofilm,
- the prolonged persistence of *Staphylococcus aureus* in osteoblasts according to some studies,
- escaping the immune defense mechanism.

This biofilm spreads to all the material surface in a few days explaining why a late surgical lavage is inefficient beyond 15 days. These physiopathological facts account for the need to remove the prosthetic material, most of the time, and even the more so if:

- the infection is old,
- the implant is loose,
- the patient's immune state is weak.

3.1.2 Experimental infections

Experimental studies dealing with infections on osteosynthesis material are rare because they are difficult to implement. In gram-positive models and especially staphylococcus, rifampicin seems to be recurrently chosen for most combinations. Further more, animal models have validated the prescription of oral antibiotherapy in the course of bone infection, especially with fluoroquinolones.

3.2 <u>What are the specificities of surgical treatment?</u>

3.2.1 What are the specificities of surgical treatment for an infected joint prosthesis?

It is recommended to reach three objectives in the surgical management of an infected prosthesis **(expert advice)** :

- eradicate the infection,
- save bone,
- preserve the function.

3.2.1.1 Conservation of the prosthesis

It is recommended to use synovectomy and lavage («debridement») in the case of very recent infection (post-operative until D15, recent secondary infection without loosening) **(grade C)**. The benefit is correlated to an early treatment.

It is recommended to perform total circumferential and peri-prosthetic excision, removing the neocapsule, the neosynovial membrane until obtaining a healthy well-vascularized tissue. Prosthesis dislocation and cleaning of the prosthetic interline are recommended. In the case of septic surgery, the positivity (with the same bacterium or another) of drainage fluids in culture (sent to the bacteriology laboratory after no more than 72 hours) seemed linked to a higher risk of infection relapse or recurrence **(level 2).**

It is recommended not to use lavage irrigation.

It is recommended to initiate antibiotherapy as soon as bacteriological samplings have been made, first in a probabilistic way, then adapted to documentation. The recommended course length is 6 weeks. It is useless to prolong beyond this. The persistence, at this time, of clinical and/or biological signs should lead to removing the osteosynthesis material except if there are contra-indications linked to the patient's terrain. In the best of cases, the success rate ranges between 59 and 85% **(level 4).**

It is recommended not to perform arthroscopic synovectomy at the knee level **(grade C).**

3.2.1.2 Removal of implants

3.2.1.2.1 Initial evaluation

It is recommended to make an initial evaluation which should take into account:

- the patient's cutaneous state,
- the global function,
- the state of the bone,
- the infectious state,
- associated co-morbidities.

3.2.1.2.2 Surgery

3.2.1.2.2.1 Choosing the surgical approach

It is recommended to use the previous surgical approach provided it can be extended. For the knee, it may be necessary to use a flap technique (most often local).

3.2.1.2.2.2 Removal of implants

3.2.1.2.2.2.1 Hip

Removal of the femoral implant

Femoral implants can be extracted by endo-femoral route or by femorotomy.

Endo-femoral route

It is not recommended to use mechanical extraction methods of cement with intracanalar devices because of the risk to use wrong routes or of fractures. It is mandatory to make sure all the material is removed and to check the quality of surface cleaning.

Femorotomy

It is recommended to choose femorotomy rather than the anterior distal window to improve the removal of cement. It is recommended to perform femorotomies with large vascularized bone fragments, to carefully close the femorotomy, and to osteosynthesize it with strong cerclage. After femorotomy, a cement spacer may be used.

Removal of the acetabular implant

In case of intra-pelvic implant dislocation, of protrusion without bone barrier, or intra-pelvic foreign bodies, it is strongly recommended to asses cases with vascular risk. To do so, it is strongly recommended to perform a pre-operative arteriography or an angioscan (problem of artifacts induced by the prosthesis) **(expert advice)**. It may be necessary to plan a specific surgical approach.

3.2.1.2.2.2.2 Knee

Removal of infected implants does not present any specific problem.

3.2.1.2.2.2.3 Other joints

Published data does not allow to determine any specific recommendation. The principles used for the hip and knee should be extrapolated.

3.2.1.2.2.3 Principles of reconstruction

3.2.1.2.2.3.1 Using a graft

The analysis of published data indicates that reconstruction with compacted or structural bone allograft does not induce a higher infectious or mechanical risk **(level 4).**

3.2.1.2.2.3.2 Influence of the fixation mode on the evolution of infection

• *In case of a two-step procedure*: it is possible to rebuild with a cemented or non-cemented prosthesis without observing any significant difference in terms of failure for an infectious cause **(grade C).**

• *In case of a one step procedure*: there is no recommendation on the use or not of a cemented prosthesis.

• *If a cemented prosthesis is used*: it is strongly recommended to use a cement containing antibiotics, at least because of its antibioprophylactic properties **(grade B)**.

3.2.1.2.2.3.3 Hip reconstruction

Acetabulum

The acetabular reconstruction of an infected total hip prosthesis is similar to that of a non-infected prosthesis. Restoring the center of the hip in the most physiological position is recommended **(grade C).**

Femoral implant

As for acetabular reconstruction, there is no specificity compared to the non-infected prosthesis.

3.2.1.2.2.3.4 Knee reconstruction

There is no specificity compared to the non-infected prosthesis.

3.2.1.2.2.3.5 Reconstruction of other joints

Published data does not allow to determine any specific management. The principles used for the hip and knee may be extrapolated.

3.2.1.2.3 Surgery in one or two procedures?

3.2.1.2.3.1 Indications

The published results do not allow to objectively define indications for replacement in 1 or 2 procedures.

3.2.1.2.3.2 What can be the choice criteria?

The certitude to have identified the bacterium

It is preferable to choose a single procedure surgery.

The bacterial profile

A bacterium for which antibiotherapy is limited (multi-resistant bacterium, *Pseudomonas aeruginosa*), a mycobacterium, a fungus are indications for surgery in two procedures.

Knowledge of the terrain

It does not constitute a rational criterion but it seems that a patient with a long history of prosthesis infection is not a good candidate for surgery in one procedure.

Problems with anesthesia

If the patient cannot undergo two surgeries in a given time, a single surgery should be chosen after discussion with the anesthesiologist, the surgeon, and the patient (or his family).

3.2.1.2.3.3 Modalities surgery in the two procedures

It consists in removing the prosthesis, performing the microbiological samplings in the absence of any antibioprophylaxis and antibiotherapy as described in paragraph 2.4, then in initiating antibiotherapy first probabilistic then guided by bacteriological documentation before re-implanting the prosthesis. The delay between removal and replacement of the prosthesis is variable and we can speak of «removal-replacement» in 2 short steps or 2 long steps.

What is the ideal delay for replacement?

There is no answer in the literature.

• *In case of 2 short steps*, the recommended delay is between 4 and 6 weeks during which antibiotherapy is given. The criteria for re-implantation are normality of clinical signs and biological parameters (SR and

CRP). Re-implantation of the prosthesis is performed without interrupting antibiotherapy and requires performing bacteriological and histological samplings which, if they are negative after 15 days of culture, will allow to interrupt the treatment.

• *In case of 2 long steps*, the delay may range from 3 to 6 months knowing that after 3 months replacement will be technically difficult and that in terms of function, the result will be less good. The antibiotherapy must be interrupted for 15 days before replacement. The usefulness of performing a puncture before replacing the prosthesis is not confirmed. The antibiotherapy will be resumed post-operatively after performing bacteriological and histological samplings. It should be stopped if the culture is negative (after 15 days).

Using a spacer

It is recommended with an essentially mechanical aim so as to facilitate replacement of the prosthesis.

3.2.1.2.4 What are the solutions in case of non-replacement of the prosthesis?

The patient should be explained the advantages and drawbacks of each option so as to take part in the final decision.

3.1.2.4.1 For the hip: 4 solutions are recommended**:**

- *hip resection*: this is a simple technique but limiting extreme mobility of the hip and resulting in an important difference in length;
- *trochanter iliac coaptation*: the interposition of the trochanter under the roof of the acetabulum allows to increase the stability and to limit length difference;
- *rested on resection*: it consists in making a contact between the lesser trochanter and the acetabulum. It is recommended in a multi-operated patient with the possibility to use crutches;
- *hip disarticulation:* difficult to use a prosthesis.

3.1.2.4.2 For the knee : 3 solutions are recommended:

- *resection* with support in a splint;
- *femoro-tibial arthrodesis*: to obtain fusion, an external fixator can be used or a femoro-tibial pin which is supposed to be more reliable;
- *amputation of the thigh*.

3.2.1.3 What are the treatment specificities of infected shoulder prosthesis?

The most commonly documented bacterium is *Propionibacterium acnes*, a commensal bacterium of the axilla.

The one step replacement of the prosthesis is recommended because of a better functional result **(grade C)**. When a prosthesis cannot be replaced (especially in case of septic reversed prosthesis) it is recommended to perform an arthroplastic resection. This solution has a mediocre functional result but a good analgesic result.

3.2.2. What are the specificities of surgical treatment for infected pseudarthrosis?

An infected pseudarthrosis must be managed in 3 operative steps:

3.2.2.1 Excision

It is recommended to perform excision of necrotized tissues and to remove all the osteosynthesis material **(grade A).** The excision must have for limit the vascularized bone **(grade C).** It often creates a «resection cavity". This cavity may be filled during surgery with acrylic cement beads or with a cement block, or in the same procedure with a bone graft. If cement is used, it is recommended to use the antibiotic impregnated cement **(grade C).** Systemic antibiotherapy adapted tor the results of surgical sample assessment is normally used for a mean duration of 6 weeks **(grade C)**.

3.2.2.2 Stabilization

It is usually recommended to use an external fixator **(grade C)**. The pins will be inserted far from the infected bone focus. It is recommended to use a monoplane external fixator system. In some cases if infection is controlled, it is possible to use internal osteosynthesis.

3.2.2.3 Reconstruction

It can be performed in one or two procedures; in the latter case a delay of around 6 weeks after initial debridement is recommended.

3.2.2.3.1 Cancellous bone autograft

It is the best means of reconstruction for an Infected resection. For the lower limb, it is a good solution to use a great mass of cancellous bone (by using the fibula) which allows for partial skin coverage, and may shorten cutaneous recovery. It is recommended not to use open cancellous graft unless specifically indicated (Papineau's technique) **(grade C)**.

It is recommended not to perform reconstruction with cortical or cortical cancellous bone. It is recommended not to use bank bones or bone substitutes for reconstruction.

3.2.2.3.2 Skin coverage

It is strongly recommended cover bone reconstruction **(grade B)**. Cutaneous closure without tension is mandatory. It can be achieved primarily, often the case for the femur; or for the lower limb, use local coverage flaps or exceptionally remote flaps. A vacuum aspiration bandage is another type of guided healing, the cost-benefit of which has not been assessed yet.

3.2.3 What are the specificities of surgical treatment for chronic osteitis on bone without loss of cortical continuity?

It is recommended to manage this infection with the 3 operative steps: excision, filling, coverage.
The requirements for excision are the same as for infected pseudarthrosis (cf.3.2.2.). It exposes to the risk of weakening, which may require using osteosynthesis according to the same principles as for infected pseudarthrosis (cf.3.2.2.).
The principles of filling and coverage are the same as for infected pseudarthrosis.

3.2.4 What are the specificities of surgical treatment for vertebral infections?

Infections on rachis osteosynthesis material raise two specific problems:

- the diagnosis is difficult because of the depth of the operative site,
- there is a mechanical risk because of the usual slow fusion process.

Literature data suggests only a proof level of **4**.
Infection in case of rachis surgery with osteosynthesis material raises three questions:

- Is there discal involvement?
- Is there a meningeal breech? Is there meningitis?
- Is there medullar compression?

If discal involvement is suspected, it is recommended to perform a per-cutaneous biopsy with samples for the bacteriology and anatomopathology laboratories. The onset or aggravation of neurological signs (meningeal syndrome, consciousness disorders, etc.) should suggest the diagnosis of meningitis and impose emergency surgery.
In all cases, it is recommended to drain the deep or epidural abscess and perform debridement:

- *if the infection is early or delayed* (occurring between surgery and the third month), it is recommended to excise all the possibly infected tissues up to healthy and well-vascularized tissue. All the cavities must be opened. The grafts should be washed and reimplanted unless they are necrotized. If the implants are stable, it is advised to leave them *in situ* because they will facilitate consolidation;
- *if the infection is late* (after the third month), consolidation is usually acquired (between month 3 and 6) and it is recommended to remove the material.

It is difficult to suggest a consensual therapeutic management for infections occurring on intersomatic cage or on disk prosthesis. Nevertheless, exeresis seems difficult in this case. Infections on posterior lumbar ligaments should lead to their excision because of their superficial localization.

3.2.5 What are the specificities of surgical treatment for septic post-operative arthritis?

3.2.5.1 Arthritis associated to a joint fracture with material

At the effusion stage, without any significant synovitis, it is recommended to perform articular lavage.

At the synovial stage, it is recommended to perform synovectomy which may need to be repeated **(grade C)**. In case of osteoarthritis, there is no consensual recommendation. The material must be removed if it is no longer necessary; otherwise, it must be washed if it is stable, changed if it is not stable.

The contribution of arthroscopy has not been determined yet (which is not the case for arthritis on a native joint).

3.2.5.2 Knee arthritis and ligamentplasty

Several therapeutic options are used. It is recommended to perform arthroscopic lavage which may be associated to synovectomy. Ligamentplasty should be preserved if possible. Nevertheless, it is sometimes necessary to remove fixation devices (interference screw, cortical screw) **(grade C)**.

3.2.6 What should be done when the external fixator is infected?

Infection on the pins of an external fixator fall into two categories: minor infections for which conservative treatment is recommended and major infections for which removal of the infected pin is required (addendum 3).

3.2.6.1 What are the means to diagnose a external fixator pin infection?

3.2.6.1.1 Clinical signs

It is recommended to check for erythema around the pin, for pus discharge, or local pain.

3.2.6.1.2 Biological data

It is recommended to follow evolution of CRP, if there is no other infection.

3.2.6.1.3 Bacteriological data

Sampling of the discharge around the external fixator pin is contraindicated. After antiseptic cleaning of the pin outlet, it is recommended to use a syringe fitted with a catheter to draw purulent fluid along the incriminated pin. In case of insufficient fluid discharge, it is possible to inject saline along the pin and to draw it back before sending it to the bacteriological laboratory.

3.2.6.1.4 Imaging

Radiographic imaging of the pin with several views is recommended so as to screen for osteolysis around the pin.

3.2.6.2 What treatment is suggested?

Therapeutic protocols are not all consensual, but they all agree on using conservative treatment for minor infections and removal of the infected pin for major infections.

There are three major presentations **(grade C)**:

- *in case of local inflammation* (localized redness without discharge or osteolysis), it is recommended prescribe rest and optimization of local antiseptic care (local antibiotherapy is not recommended);
- *in case of discharge* (local inflammation associated to discharge without osteolysis), it is recommended to perform bacteriological sampling according to the technique described in paragraph 3.2.6.1.3. Then, it is recommended to prescribe rest and local antiseptic care. It is recommended to associate antibiotherapy adapted to the results of bacteriological sample assessment. The length of antibiotherapy is not codified;
- *in case of osteolysis* (local inflammation associated to pus discharge and radiologically proven osteolysis), it is recommended to remove the pin, to excise its pathway tissue with curettage, and to send the pin and surgical samples to the bacteriological laboratory. Antibiotherapy adapted to the bacteriological documentation is advised for 6 weeks. It the external fixator is no longer needed, it is recommended to remove it completely. If it is still needed, another pin should be added in a healthy zone, or the whole external fixator should be changed so as not to disrupt the orthopedic set-up.

3.3 What are the specificities of anti-infectious treatment?

3.3.1 What is the contribution of local antibiotherapy?

It is recommended to use cements with antibiotics only temporarily, either for the filling of an infected cavity, or to change a prosthesis with surgery in two procedures.

3.3.1.1 Types of cement with antibiotics

Strong doses of antibiotics may need to be used for therapy. This type of cement is prepared by the surgeon extemporaneously in the operating room.

These types of cement are only recommended temporarily in two presentations:

- cement beads used to fill a cavity. These are impregnated with antibiotics, they have a local action for the first weeks. They will be removed secondarily;

- spacer with cement impregnated with antibiotics, with the objective on one hand to maintain the space after removing the implant and, on the other hand, to obtain local antibiotherapy thanks to high doses of antibiotics.

These cements must in no case dispense from a prescription of general antibiotherapy.

3.3.1.2 Pharmacokinetics of this local antibiotherapy

The kinetics of antibiotic release includes two phases: an immediate phase during 7 days, due to a high concentration of antibiotics and a secondary phase, for the years during which much weaker doses of antibiotics are present (sub-inhibiting doses).

The antibiotics used in cement are currently aminosides, vancomycin, and clindamycin.

3.3.2 What systemic antibiotherapy should be used, how should it be administered, for what length, what surveillance ?

3.3.2.1 General principles

The prescription of antibiotherapy for bone and joint infections on material is subject to some rules:

- document the infection (in case of sepsis [addendum 2], antibiotherapy must be initiated in a probabilistic manner after collecting microbiological samples and before obtaining the results),
- antibiotherapy initiated as a combination;
- achieving high plasmatic concentrations;
- using molecules with a good bone distribution;
- in case of infection due to staphylococci, never use rifampicin, fusidic acid, fluoroquinolones, and fosfomycin in monotherapy;
- linezolide, daptomycin, tigecyclin do not have government approval in 2009, for the treatment of bone and joint infections **(grade C)**.

3.3.2.1.1 Mode of administration

It is recommended to administer the treatment initially intravenously. No study has validated the duration of parenteral antibiotherapy. It is usually 15 days long **(expert advice).** After this, it is recommended to switch to per os administration under the condition that:

- the antibiotics have a good bioavailability and a good bone distribution,
- digestive tolerance of treatment be good
- to be sure of observance. To this en, it is recommended to inform the patient of secondary adverse effects of treatment and that he will benefit from scheduled consultations to assess the therapeutic observance.

When using antibiotics with a strong bioavailability and meeting these criteria, it is possible to prescribe antibiotics per os earlier so as to decrease the length of intravenous du treatment **(expert advice)**.

It is recommended not to associate antibiotherapy to gastric ulcer treatment and to iron supplementation do to a bad absorption of some of these antibiotics. It is recommended to check the absence of drug interaction between antibiotics and other ongoing treatments **(expert advice)**.
If switching to oral treatment is impossible (glycopeptides, ceftazidim, ureido and carboxy-penicillins, carbapenems), it is mandatory to find a way to maintain parenteral antibiotherapy as long as necessary, either in hospital or in ambulatory treatment **(grade C)**.
In this case, it is recommended to insert a central catheter which may be changed if the planned duration of antibiotherapy is inferior to 6 weeks, or a totally implanted central venous access device (TICVAD) if the planned duration of antibiotherapy is superior to 6 weeks. The device must be removed at the end of treatment if it is a central catheter and in an average of 3 months after the end of antibiotherapy in case of a TICVAD.

3.3.2.1.2 Antibiotic combinations

It should be maintained as long as possible **(grade B)**.
In case of staphylococcal infection, the combination should be maintained for at least 6 weeks (using rifampicin preferably in the combination scheme if the bacterium is susceptible and under the condition that rifampicin never be used in monotherapy) **(grade B)**.
In case of Gram-negative infection, streptococcus or enterococcus, the duration of combination therapy is not clearly defined. It depends on the molecules prescribed. It is recommended not maintain aminoside treatment beyond 7 days **(grade C)**.

In case of *Pseudomonas aeruginosa* infection, the combination should be maintained for at least 3 weeks **(grade C)**.
In case of anaerobic infection, the contribution of antibiotic combination has not been demonstrated.

3.3.2.1.3 Total length of treatment

It is recommended to administer antibiotic treatment for a minimum of 6 weeks. The usual length of treatment reported in literature is 6 to 12 weeks. Maintaining antibiotherapy beyond 12 weeks should be discussed **(expert advice).**

3.3.2.1.4 Surveillance of antibiotherapy

It is recommended to survey the effectiveness and tolerance of antibiotherapy.
• The effectiveness is assessed first on clinical data then on biological parameters (essentially CRP). It is recommended to dose antibiotics for which there are important inter-individual variations of blood concentrations which can lead to prescribing maximal dosage. It is thus recommended to dose aminosides (at the peak) and glycopeptides. If rifampicin is used and because of its enzymatic induction potential, it is advised to check with pharmacological dosage that the antibiotic to which it is combined is not under dosed. It should be noted that rifampicin decreases by half plasmatic concentrations of clindamycin (dosing clindamycin is recommended); this may lead to important under-dosage of clindamycin whether administered *per os* or intravenously.

• *Tolerance* is assessed by taking patient history and with biological parameters (CBC/platelets, hepatic biological assessment, renal function). It is also necessary to measure blood concentrations of some antibiotics such as aminosides (trough level).

3.3.2.2 Choosing molecules according to the pathogen

3.3.2.2.1 Staphylococcal infections

The therapeutic suggestions are presented in tables III (infection with staphylococcus susceptible to methicillin) and IV (infection with staphylococcus resistant to methicillin). In case of staphylococcus strains resistant to methicillin, determining the MIC with glycopeptides is essential. For those with decreased susceptibility to glycopeptides (MIC ≥ 4 µg/l), only vancomycin, among glycopeptides, remains efficient (CMI ≤ 8 µg/ml). In this case, using other antibiotics (linezolide, daptomycin) may be considered after consulting a referent infectiologist.

When prescribing vancomycin for severe sepsis (in case of infection with a staphylococcus resistant to methicillin or in case of allergy to penicillin), it is recommended to combine it with gentamycin from 48 to 72 hours because of the time needed to reach efficient blood concentrations of vancomycin **(expert advice)**.

3.3.2.2.2 Infections with streptococcus and enterococcus

In case of infection with a beta-hemolytic streptococcus, amoxicillin remains the molecule of choice. In case of non-groupable streptococcus, determining the MICs of beta-lactams is recommended to choose the optimal antibiotherapy. It is possible to combine it with gentamycin for 5 to 7 days (if the resistance level is low). The treatment will then be continued with amoxicillin in monotherapy **(grade C)**.

In case of infection with an enterococcus , amoxicillin is the reference treatment. It is possible to combine it with gentamycin for 5 to 7 days (if the resistance level is low) then to replace the aminoside by rifampicin while maintaining amoxicillin **(expert advice).** In case of an enterococcal strain resistant to beta-lactams, it is recommended to use a glycopeptide.

The therapeutic suggestions are presented in table V.

3.3.2.2.3 Infections with Gram negative bacilli

It is recommended to use a combination of beta-lactams and fluoroquinolones if the strain is susceptible. If the strain is resistant to fluoroquinolones, the molecule will be replaced by an aminoside. In case of severe sepsis or septic shock (addendum 2), it is recommended to use a combination of beta-lactam and aminoside. Switching to fluoroquinolones may be initiated in monotherapy if the strain is susceptible and if there is no strong bacterial inoculum (presence of pus at surgery).

In case of infection with *Pseudomonas aeruginosa*, it is recommended to use a combination of active molecules such as ceftazidim or cefepim, or a carbapenem (except for ertapenem) with amikacin, or tobramycin, or ciprofloxacin, or fosfomycin. The combination must be maintained for at least 3 weeks. In case of aminoside prescription, renal and auditive toxicity must be taken into account (monitoring of residual plasmatic levels). Switching to ciprofloxacin may be initiated in monotherapy if the bacterium is susceptible, if the patient benefited from an efficient initial bi-antibiotherapy and an optimal surgical management and if the therapeutic observance and the dosage were sufficient **(expert advice)**.

The therapeutic suggestions are presented in table VI.

3.3.2.2.4 Infections with anaerobic bacteria

There is no published study allowing to give recommendations. No data shows the contribution of antibiotic combinations.

Clindamycin and metronidazole may be used parenterally or per os with a high bone distribution. The weak activity of clindamycin on *Bacteroides* and the lack of metronidazole activity on *Propionibacterium acnes* should be acknowledged.

The therapeutic suggestions are presented in table V.

Table III: suggestions for antibiotherapy in case of infections with staphylococci susceptible to methicillin, adapted to the antibiogram and the terrain

	Absence of allergy to penicillin	**If allergy to penicillin**
Initial IV antibiotherapy (2 weeks)	(oxacillin or cloxacillin) **or** cefazolin + gentamycin[1] **or** rifampicin	clindamycin (if the strain is susceptible to erythromycin) **or** (teicoplanin or vancomycin) + gentamycin[1] or rifampicin[2] **or** (teicoplanin or vancomycin) + fusidic acid
Switching to oral route	rifampicin + (ofloxacin or pefloxacin[3] or ciprofloxacin or levofloxacin[4]) **or** rifampicin + fusidic acid[5] **or** rifampicin + clindamycin[2] (if the strain is susceptible to erythromycin) **or** (ofloxacin or pefloxacin[3] or ciprofloxacin or levofloxacin[4]) + fusidic acid **or** clindamycin (if the strain is susceptible to erythromycin) + fusidic acid **or** rifampicin + cotrimoxazole (if there is no other alternative)	

1: Maximal length of prescription: 5 to 7 days.

2: Rifampicin decreases by half blood concentrations of clindamycin; this may lead to important under dosing of clindamycin whether per os or intravenously (dosage of clindamycin is recommended).

3: Refer to AFSSAPS recommendations.

4: The prescription of levofloxacin in this indication is not government approved and must be validated by a referent infectiologist.

5: This combination requires a regular surveillance of liver function.

Table IV: suggestions for antibiotherapy in case of infections with staphylococci resistant to oxacillin, adapted to the antibiogram and the terrain, except for strains with intermediate susceptibility to glycopeptides (MIC ≥ 4µg/ml)

Initial IV antibiotherapy (2 weeks)	(vancomycin[1] or teicoplanin[2]) + rifampicin[3] **or** (vancomycin[1] or teicoplanin[2]) + fusidic acid[3]. **or** (vancomycin[1] or teicoplanin[2]) + fosfomycin **or** (vancomycin[1] or teicoplanin[2]) + doxycyclin **or** clindamycin (if the strain is susceptible to erythromycin) + gentamycin[4] **then** clindamycin + rifampicin[5]
Switching to oral route if the bacterium susceptibility allows it	rifampicin + fusidic acid[6] **or** rifampicin + clindamycin[5] (if the strain is susceptible to erythromycin) **or** rifampicin + cotrimoxazole **or** rifampicin + (minocyclin[7] or doxycyclin) **or** rifampicin + linezolid[8]

1: To obtain the maximal effectiveness of glycopeptides for the treatment of bone and joint infections, it is mandatory to use vancomycin in continuous IV infusion with an infusion pump.

2: Teicoplanin can only be used after determining the MIC.

3: If a glycopeptide is combined with fusidic acid or with rifampicin, it is advised to delay the prescription of these two molecules by 48 hours so as to have sufficient blood concentrations of glycopeptide.

4: Maximal length of prescription: 5 to 7 days.

5: Rifampicin decreases by half blood concentrations of clindamycin; this may lead to important under dosing of clindamycin whether per os or intravenously (dosage of clindamycin is recommended).

6: This combination requires a regular surveillance of liver function.

7: Minocyclin (refer to AFSSAPS recommendations) has a better MIC than doxycyclin but is less well tolerated.

8: Linezolid is not government approved for this indication. It must be prescribed only in case of documented infection and under close clinical and biological surveillance, without more than 28 days of treatment (hematological and neurological toxicity; especially in patients > 58 years of age). Its prescription must be validated by par a referent infectiologist.

Table V: suggestions for antibiotherapy in case of infections with streptococci, enterococci, anaerobes, adapted to the antibiogram and the terrain

Streptococci	**Absence of allergy to penicillin**	**If allergy to penicillin**
Initial IV antibiotherapy	amoxicillin + gentamycin[1]	clindamycin (if the strain is susceptible to erythromycin) + gentamycin[1] **or** cefazolin + gentamycin[1] **or** ceftriaxone + gentamycin[1]
Switch to oral route	amoxicillin **or** clindamycin (if the strain is susceptible to erythromycin)	
Enterococci		
Initial IV antibiotherapy	amoxicillin + gentamycin[1] **then** amoxicillin ± rifampicin	(vancomycin[2] or teicoplanin) + gentamycin[1] **then** (vancomycin[2] or teicoplanin) + rifampicin
Switch to oral route	amoxicillin ± rifampicin	Expert advice
Gram (+) anaerobes *(P. acnes, Peptostreptococcus)*	amoxicillin **or** cefazolin **or** ceftriaxone **or** clindamycin (if the strain is susceptible to erythromycin)	clindamycin
Gram (-) anaerobes *(Bacteroides spp...)*	clindamycin **or** metronidazole[3] **or** amoxicillin- clavulanic acid	clindamycin **or** metronidazole[3]

1: Maximal length of prescription: 5 à 7 days.

2: To obtain the maximal effectiveness of glycopeptides for the treatment of bone and joint infections, it is mandatory to use vancomycin in continuous IV infusion with an infusion pump.

3: No activity on *P. acnes.*

Table VI: suggestions for antibiotherapy in case of infections with Gram-negative bacilli adapted to the antibiogram and the terrain

Initial IV antibiotherapy *Pseudomonas aeruginosa*	(cefotaxim or ceftriaxone) + (ciprofloxacin or ofloxacin) **or** (cefotaxim or ceftriaxone) + gentamycin[1] **or** (imipenem or meropenem[2] or doripenem[2]) + gentamycin[1] (ceftazidim or cefepim) **or** (imipenem or meropenem[2] or doripenem[2]) + (amikacin[1] or tobramycine[1]) **or** ciprofloxacin **or** fosfomycin
Switch to oral route (if the strain is susceptible to fluoroquinolones and in the absence of a high bacterial inoculum)	ofloxacin **or** ciprofloxacin if *Pseudomonas aeruginosa*

1: Maximal length of prescription: 5 à 7 days.

2: Not government approved. The prescription must be validated by a referent infectiologist.

3.3.2.2.5 Probabilistic antibiotherapy

It is the antibiotic scheme to recommend before obtaining per operative bacteriological results when there is no reliable documentation in the patient's history and when there are general signs indicating the emergency of treatment. Several combinations of antibiotics can be used. They must be adapted according to the microbial ecology of each institution.

The following combinations are suggested by order of preference **(expert advice)**:

1 - ureidopenicillin/ beta-lactamase inhibitor + vancomycin

2 – 3rd generation cephalosporin + vancomycin

3 – carbapenem (except for ertapenem) + vancomycin

4 – 3rd generation cephalosporin + fosfomycin.

3.3.2.2.6 Suppressive antibiotherapy

It consists in maintaining antibiotherapy per os for an undetermined length so as to inhibit bacterial growth around the prosthesis.

It applies to situations for which the bacterium is documented and the infection persists in an inoperable patient with a non-loosened prosthesis. It can be used only with well-tolerated molecules and easy administration (per os) **(grade C)**.

3.3.2.2.7 Modes of administration, dose of antibiotics

They are presented (for a normal renal and hepatic function) with surveillance of blood concentrations in tables VII and VII bis.

Table VII: doses and ways of administration of antibiotics used for bone and joint infections on osteosynthesis material

Antibiotics (DCI)	**Dose/24h**	**Regimen**
amoxicillin	100-200 mg/kg	4-6 injections IVL 3-4 oral intakes
cloxacillin oxacillin	100-200 mg/kg (doses superior to approval – expert advice)	4-6 injections IVL
amoxicillin- clavulanic acid	100 mg/kg	4-6 injections IVL 3-4 oral intakes
cefazolin	60-80 mg/kg	4-6 injections IVL or Infusion pump[1]
cefotaxim	100-150 mg/kg	3 injections IVL
ceftriaxone	30-35 mg/kg	1-2 injection(s) IVL
ceftazidim	100 mg/kg	Infusion pump[1] or 3-4 injections IVL
imipenem	2 à 3 g	3 to 4 administrations IV or IM
meropenem	3 à 6 g	3 administrations IV
vancomycin[2]	40-60 mg/kg	Infusion pump[1]
teicoplanin[2]	12 mg/kg/12h for 3-5 days then 12 mg/kg	IVL, IM or s/c
gentamycin[3]	3-4 mg/kg	1 administration IV 30 minutes
amikacin[3]	15 mg/kg	1 administration IV 30 minutes

Table VII bis: doses and ways of administration of antibiotics used for bone and joint infections on osteosynthesis material

Antibiotics (DCI)	Dose/24h	Regimen
ofloxacin	400-600 mg	2 à 3 oral intakes 2 à 3 injections IVL
pefloxacin	800 mg	2 oral intakes 2 injections IVL
levofloxacin (not government approved)	500 à 750 mg	1 oral intake 1 injection IVL
ciprofloxacin	1,500-2,000 mg 800 à 1,200mg	2 to 3 oral intakes 2 to 3 injections IVL
clindamycin	1,800-2,400mg	3-4 injections IVL 3 oral intakes
rifampicin	20 mg/kg	2 administrations IV 30 minutes 2-3 oral intakes
fusidic acid	1,500 mg	2-3 oral intakes 2-3 injections IVL
fosfomycin	150-200 mg/kg	3-4 administrations 120 minutes
cotrimoxazole	3,200 mg/640 mg	2 oral intakes 2 injections
minocyclin doxycyclin	200 mg	2 oral intakes 2 injections IV (doxycyclin)
linezolid (not government approved)	1,200 mg	2 oral intakes 2 injections IVL

1- infusion pump: begin with a loading dose (1/4 or 1/3 of the dose per 24 hours) to inject in 1 hour for vancomycin or IVL for cefazolin or ceftazidim, then connect continuous infusion immediately after.

2- **dosing glycopeptides:** it must be performed after 72 hours for vancomycin and after the 6th infusion for teicoplanin (just before infusion), then once a week during all the treatment. The expected blood concentrations must range between 30 and 40µg/ml for vancomycin in continuous infusion and in trough level (Cmin) for teicoplanin.

3- **Cmax**: should be assessed 1 hour after the beginning of infusion, after 72nd hour; **Cmin**: should be assessed just before infusion, after 72nd hour.

3.3.3 Prosthetic device fungal infection

There is no randomized assay in the literature allowing for a reliable proof level.

3.3.3.1 What are the modalities of therapeutic management?

In case of fungal infection on a joint prosthesis, it is recommended to remove the prosthesis as well as any adjacent material **(expert advice).**

It is recommended to replace the prosthesis after the end of antifungal treatment **(expert advice).**

In case of infection on osteosynthesis non-prosthetic material, it is recommended to remove all the material.

3.3.3.2 Antifungal treatment

3.3.3.2.1 *Candida* infection

It is recommended to use amphotericin B IV for at least 15 days **(grade C).** In case of bad tolerance or renal insufficiency, it is possible to use amphotericin B in its liposomal presentation. It is possible to use it in a combination with 5-fluorocytosine in case of a susceptible fungal strain and without contraindication **(expert advice)**.

After 15 days, it is recommended to switch to fluconazole per os if the fungal strain is susceptible. If it is resistant, the alternative is voriconazole per os **(expert advice)**.

It is recommended to maintain antifungal treatment from 3 to 6 months in an immunocompetent patient **(grade C).** In case of severe immunodepression, it is recommended to maintain treatment with a secondary prophylaxis at the same dose throughout immunodepression.

3.3.3.2.2 *Aspergillus* infection **(grade C)**

It is recommended to use voriconazole per os or IV in first intention. In case of contraindication, it is recommended to use parenteral amphotericin B.

It is recommended to maintain treatment for at least 6 months in an immunocompetent patient. In case of severe immunodepression, it is recommended to maintain treatment with a secondary prophylaxis at the same dose throughout immunodepression.

The therapeutic suggestions are presented in table VIII.

Table VIII: suggestions for antifungal treatment of *Candida* and *Aspergillus* bone and joint infections on material

Antifungal family	International Nonproprietary Name (*INN*)	Dose/24 h and route	Indications
Polyenes	amphotericin B	0.7-1 mg/kg IV	*Candida* *Aspergillus*
Nucleotide analogue	5-Flucytosine	100-200 mg/kg* IV or *per os*	*Candida* Always in combination.
Triazoles	Fluconazole	400-800 mg/d *per os* or IV	*Candida*
	Voriconazole	6 mg/kg/12 h (D1), then 4 mg/kg/12 h, IV. **Switch to oral route** Weight > 40 kgs: 400 mg/12h (D1), then 200 mg/d. Weight < 40 kgs: 200 mg/12h (D1), 100 mg/12h.	*Aspergillus* *Candida*

* recommended doses to prevent toxicity

3.3.4 What specific antibiotherapy for children with a bone and joint infection?

In early infections, the material is left place and can only be removed after bone consolidation. In late infections, the orthopedic material is removed. Other clinical presentations are upper and lower limb osteotomies and traumatology. There is no randomized controlled study of infections on osteosynthesis material in children.

The modalities of antibiotic treatment recommended in children are the same as for adults since most antibiotics may be used by taking into account doses adapted to the child's weight and restrictions linked to the child's age.

Fluoroquinolones cannot be used before 15 years of age because of their toxicity on articular cartilage, even though recent controlled studies have reported only arthralgia or transient arthritis. When a fluoroquinolone must be used in a child under 15 years of age (not government approved), the decision must be taken by the referent infectiologist after assessing the expected risk/benefit with the same restrictions as for the adult.

The modalities of antibiotic use in infants and children are summarized in tables IX and IX bis.

Table IX: suggestions for antibiotherapy in bone and joint infections on material in children (infections with staphylococci)

Micro-organisms	Antibiotics (DCI)	Administration route	Dose/24h	Nb of intakes /24 hours
***Staphylococcus aureus* or coagulase negative susceptible to methicillin**	(oxacillin or cloxacillin) **+** rifampicin **or** clindamycin	IV IV IV or PO IV or PO	150 to 200 mg/kg 150 to 200 mg/kg 20 mg/kg 40 mg/kg	4 to 6 2 3 to 4
***Staphylococcus aureus* or coagulase negative resistant to methicillin**	vancomycin + rifampicin	IV IV or PO	60 mg/kg 20 mg/kg	Infusion pump 2
Switch to oral route				
	rifampicin **+** fusidic acid **or** clindamycin **or** co-trimoxazole **or** lev*ofloxacin* (not government approved) **or** *minocyclin*	PO PO PO PO PO PO	20 mg/kg 40 à 60 mg/kg 40 mg/kg 40 to 60 mg/kg of SMX 10 mg/kg if > 5 years of age 20 mg/kg if < 5 years of age E> 8 years of age: 4 mg/kg	2 3 3 to 4 3 1 to 2 2 2

Table IX bis: suggestions for antibiotherapy in bone and joint infections on material in children (infections with streptococci, enterococci, enterobacteria, and anaerobes)

Micro-organisms	Antibiotics (DCI)	Administration route	Dose /24h	Nb of intakes /24 hours
streptococci (susceptible to penicillin)	amoxicillin **or** (ceftriaxone or *cefotaxim*)	IV IV IV	150 to 200 mg/kg 70 to 100 mg/kg 150 to 200 mg/kg	4 1 to 2 4
Switch to oral route	amoxicillin	PO	150 to 200 mg/kg	4
enterococci (susceptible to penicillin)	amoxicillin + gentamycin	IV IV	150 to 200 mg/kg 5 -7.5 mg/kg	4 1
Switch to oral route	amoxicillin	PO	150 to 200 mg/kg	4
enterobacteria	ceftriaxone or *cefotaxim*	IV IV	70 to 100 mg/kg 150 to 200 mg/kg	1 to 2 4
Switch to oral route	*ciprofloxacin* (hors AMM)	PO	20 à 30 mg/kg	3
Pseudomonas aeruginosa	*ceftazidim* **+** amikacin **or** *ciprofloxacin* (not government approved)	IV IV IV or PO	60 mg/kg 15 mg/kg 20 à 30 mg/kg	4 or Infusion pump 1 2 or 3
anaerobes	clindamycin	IV or PO	40 mg/kg	4

3.4 What other medical management may be used (pain management, rehabilitation, medico-psycho-social management)?

3.4.1 Management of pain

It is mandatory to manage the patient's pain from the day of surgery and throughout rehabilitation by consulting, if necessary, a pain management center.

3.4.2 What is the contribution of rehabilitation?

If it is probable that a bone and joint infection on material may be diagnosed during the rehabilitation stay:

- it is strongly recommended not to prescribe probabilistic antibiotherapy and especially after performing skin or wound sampling **(grade C)**,
- it is strongly recommended to warn the surgeon **(grade C)**,
- it is recommended that the physiotherapist take part in setting up the therapeutic strategy, within the multidisciplinary team **(grade C).**

What organization should be suggested for a patient with bone and joint infection on material under treatment and staying in a rehabilitation center?

It is recommended to maintain rehabilitation with hygiene measures such as standard precautions, sometimes associated to complementary hygiene measures such as «contact» precautions for patients presenting a high risk of multi-resistant bacterium cross-transmission **(grade C).**

In case of high risk of cross-transmission (productive non-healed surgical wound, non occlusive bandage, carrier of MRB), it is recommended to place the patient in a room alone **(grade C)** which does not exclude going out of the room if «contact» precautions are observed. This must not impair the quality of rehabilitation **(grade C)**.

If the patient presenting a high risk of multi-resistant bacterium cross-transmission is rehabilitated in his room, hygiene measures such as «contact» precautions must be observed with single use material if available, and dedicated rehabilitation material if possible, otherwise strict cleaning-disinfection of materials must be performed between two patients.

If the patient presenting a high risk of multi-resistant bacterium cross-transmission has access to the rehabilitation room, the program must be set-up so that cleaning-disinfection of materials be adequately performed between two patients and «contact» precautions be observed and known by all **(grade C).**

When a surgical wound is not healed, balneotherapy is contraindicated and the rehabilitation program must be adapted **(grade C).**

In case of nasal carriage and/or MRB colonization of a patient cured of infection on osteosynthesis material, it is recommended to apply the same preventive measures against cross-transmission in the rehabilitation center.

3.4.3 What is the contribution of medico-psychological management?

Medical and surgical teams managing bone and joint infections on material should collaborate with a psychiatrist or a psychologist with specific competences in managing handicap.

It is recommended to:

- be informed on the patient's psychiatric history during the first consultation,
- know about psychiatric disorders usually met in the course of bone and joint infections,
- screen for prodromes of psychic suffering,
- be able to diagnose major depression,
- suggest an adequate pharmacological and/or psychotherapeutic treatment in case of psychic disorders,
- to take into account the patient's psychic suffering and not only his somatic state,
- suggest psychological assistance to the patient in case of amputation,
- accept the presence of the psychologist and/or psychiatrist and to integrate him in the management strategy.

It is recommended to set-up a multidisciplinary organization allowing to give the patient a coherent and univocal reasoning during the medico-psychological management of bone and joint infection on material.

When psychic disorders are suspected, it is recommended to consult a psychologist or psychiatrist and mentioning to the patient that they belong to the healthcare team.

The psychologist or psychiatrist can also support the medical and paramedical teams in case of difficult situations.

The successive pieces of information given to the patient during bone and joint infections on material must observe the following rules:

- they must be given in adapted settings, with empathy,
- it is recommended that the information be given by a person who usually manages the patient and in some cases, in the presence of a third party designated by the patient,
- it is recommended to breakdown information, to prevent lying, trivialization, false reassurance, and avoiding the truth,
- it is recommended to respecter the patients defense mechanisms.

3.4.4 What is the contribution of social management?

An assessment made by a social worker before the medico-surgical management, allows to forecast the patient's future both on the familial and economic level. It is recommended to anticipate difficulties raised by removal of the material. It is thus recommended tat the social worker meet the patient and his family as

soon as the therapeutic scheme is established. This allows to plan further care ahead of time after hospitalization in orthopedics or in the infectious diseases ward:

- either by going back home, with the implementation of care, if the social context allows it,
- or by transfer to a follow-up care institution in other cases.

After replacing the prosthesis, it is recommended to evaluate the opportunity of transferring the patient to a functional rehabilitation center.

The social worker may intervene with the medical adviser in some cases, to set-up the occupational reclassification of the patient if necessary.

The family physician should submit a demand for 100% of coverage for bone and joint infections on material (not listed in long-term diseases), but this can be anticipated and scheduled by the hospital physician managing the patient.

3.4.5 What are the current propositions for the medico-surgical management and the follow-up of patients with prosthetic device bone and joint infections? What tests? What frequency? What organization and what structures? Is cure possible?

3.4.5.1 What are the current propositions for the medico-surgical management and the follow-up of patients with prosthetic device bone and joint infections?
What tests? What frequency?

3.4.5.1.1 Clinical surveillance

It is identical to that recommended in case of non-septic orthopedic surgery.

It is recommended to remove drains between 48 and 72 hours and systematically as soon as their draining function is no longer needed. It is recommended to change aspiration vials regularly observing a strict hygiene procedure so as to prevent any contamination.

3.4.5.1.2 Biological surveillance

It is recommended to use CRP as the main biological marker following surgery. This biological marker level should decrease between day 10 and 15 after surgery.

3.4.5.1.3 Surveillance with imaging

Common x-ray is the most used radiological exam to follow-up bone and joint infection on material. It is recommended to perform this examination after surgery (D2-D3), on the patient's discharge (D10-D15) then at 1 month, 3 months, 6 months, 1 year after surgery. The sequential x-rays must be available for comparison.

It is not recommended to perform other radiological examinations systematically except for specific cases.

3.4.5.2 What organization and what structures?

Organizing the management of bone and joint infections on material must allow patients to benefit from the most appropriate care for their state based on valid and regularly updated guidelines; this optimal management requires:

- an accurate clinical evaluation;
- a microbiological diagnosis requiring validated techniques both for sampling and for the identification of micro-organisms;
- a therapeutic strategy defined during multidisciplinary staff meetings grouping various professionals specialized in the management of such infections (infectiologists, orthopedic surgeons, and in some cases, vascular or plastic surgeons, rheumatologists, microbiologists, radiologists, nuclear medicine specialists, anesthesiologists-ICU specialists, physical medicine specialists, etc.);
- implementing specific treatments especially for surgical and anti-infectious goals in the short term;
- a global continuous and clear management until coming back home, with, at best, a healthcare file including the detail of medical and surgical treatments, complementary investigations, follow-up care, and rehabilitation;
- continuous information of the patient during all the healthcare process and his follow-up.

Specifications written out by six expert societies[†] in collaboration with the patient association (Le Lien), and with the expert advice of the national committee for nosocomial and associated to care infections "Comité technique des infections nosocomiales et des infections liées aux soins" (CTINILS)[†]. According to data given by the technical agency for information, and after consulting regional agencies for hospital administration "Agences Régionales d'Hospitalisation", the Ministry of Health and Sports in September 2008 decided to de label 8 interregional reference centers for the management of complex bone and joint infections, with at least one center within the interregional scheme of health organization. In 2009, it is planned to label 2 new centers, according to needs.

These centers have for mission the coordination, expertise, training, and research as well as management of the most complex bone and joint infections in collaboration with other structures. These centers must work in collaboration with all the healthcare professionals of other interregional institutions, so as to offer quality management for each patient, as close to his home as possible, in a context of trust and safety,

from common protocols. Thus, the implementation of proximity and expert advice links should allow to develop a network between reference and associated centers.

[†]*Société de Pathologie Infectieuse de Langue Française (SPILF), Société Française de Microbiologie (SFM), Société Française d'Anesthésie Réanimation (SFAR), Société Française d'Hygiène Hospitalière (SFHH), Société Française de Rhumatologie (SFR), Société Française de chirurgie orthopédique (SOFCOT).*

3.4.5.3 Is cure possible?

The infectious and functional criteria should be taken into account.

There is no criterion defining infection cure. It is recommended to follow-up patient between 1 and 2 years after the end of antibiotherapy, lapse of time supposed to be necessary for the cure of the initial infection.

The functional result is obtained by assessing mobility, pain, strength, balance, and walking.

Question 4: what are the pre-requisites to pour minimize these types of infection?

The pre-requisites to minimize this type of infections have for most already been the object of recent national recommendations.

4.1. What are the standards in terms of healthcare environment control (architecture, surgical block ventilation, dedicated rooms)? Hygiene procedures? Environmental surveillance?

4.1.1 Patient management in hospitalization units

4.1.1.1 Contribution of so-called "septic" units

There is no formal proof of their effectiveness on the prevention of SSI.

4.1.1.2 Management of potential portals of entry during care giving

It is recommended to limit the duration of urinary catheterization of, and to observe rules for asepsis when inserting one **(grade C)**.

Unless there is obvious contamination or hemorrhage, it is recommended that the bandage be made at the end of surgery in the operating room, not be removed before 24 or 48 post-operative hours, and that strict aseptic conditions be observed when making it **(grade C)**.

It is recommended to use closed aspiration systems and to avoid leaving drains in place for more than 48 to 72 hours **(grade C)**.

4.1.2 Patient management in the surgical block

It is recommended to monitor the three main factors influencing airborne biocontamination in the operating room:

- air treatment efficiency, (expert recommendation made by the French Society for Hospital Hygiène Société Française d'Hygiène Hospitalière (SFHH) published in 2004,
- healthcare personnel discipline,
- effectiveness of professional wear.

4.1.2.1 Air treatment efficiency:

SFHH experts, considered with a strong consensus, that « among the various types of surgery, the responsibility of air for SSI is the best proved in orthopedic prosthetic surgery » and that in « class 1surgery, especially with the implantation of a joint prosthesis, ventilation of the operating room with an unidirectional flux is associated to a weaker rate of SSI than with a non unidirectional flux ventilation».

4.1.2.2 Healthcare personnel discipline

It is recommended to limit the number of people in the operating room to those strictly needed for the surgery. It is recommended to limit moving around (going to and fro) of personnel in the operating room.

4.1.2.3 Professional wear and operative sheets

It is recommended that each member of the surgical team entering the operating room wear a surgery hood covering hair completely, and nose and mouth. Two pairs of gloves must be worn for the protection of surgeons in orthopedic surgery because of the frequent perforations. The second pair must be changed frequently **(grade C)**. The consensus conference «Preoperative management of infectious risk» recommended that the surgery patient be covered with a non-woven micro-fiber fabric, whatever the type of surgery and, for operative field covers, it specified that cotton fabric was no longer acceptable, because of its high particle shedding.

4.1.2.4 Managing surgical instruments

It is recommended to prepare the instrument table only after patient installation **(grade C)**.

It is recommended to pay special attention to non-sterile medical devices used per-operatively which may be soiled (non sterile anti-sore pads, tourniquet, and jersey).

4.1.2.5 Cleaning surfaces

The OR surfaces must be cleaned according to recommendations of the document dedicated to the quality of air in the operative room.

4.1.2.6 Surgical block architecture

The NF S 90-351 July 2003 standard concerning ant «clean rooms and related controlled environment» and its addenda specify the elements to take into account the conception of a surgical block to master quality of air.

4.1.2.7 Environmental surveillance

Several documents such as regulations, standards, guides, or expert recommendations suggest strategies for the monitoring of hospital environment.

Parameters to be monitored

It is recommended, for environmental surveillance, to perform microbiological controls (air, water, surfaces) and control of dust (particle cleanness and decontamination kinetics). The SFHH recommended that particle decontamination kinetics specifications be mentioned in the tests for the monitoring of performances so as to know how much time a room, equipped with air treatment, can come back to its initial state and to determine the minimal time range between two surgeries.

Indications for surveillance

The Technical Committee on Nosocomial Infections CTIN guide recommends performing microbiological controls (air, surfaces) and checking for dust in several indications:

- quality control,
- surveillance in case of construction work in dust-controlled rooms or in an adjacent zone,
- and investigation of epidemics according to the isolated microorganism (associated or not to other types of samplings).

Expected minimal performances

The level of technical performance to reach is defined in the July 2003 standard NF S 90-351 free of human presence and in the presence of equipment.

The target level recommended for surface samples is specified in the CTIN guide. Finally, the CTIN guide mentions that water quality in the operative block be checked every three months where it is delivered.

4.2 What measures should be undertaken for the preparation of the patient before surgery (antibioprophylaxis, MRB carriage, skin antisepsis)?

These measures concern preparation for an orthopedic intervention in a non-infected patient. These recommendations are **grade C**.

4.2.1.1 Specific measures for the preparation of the patient before surgery

4.2.1.2 Risk factors supposed to be without possible modification

4.2.1.3 There are no recommendations concerning risk factors supposed to be without possible modification such as, pre-operative stay in an institution, history of irradiation at the level of a surgical approach, rheumatoid polyarthritis as such, presence of cancer.

4.2.1.4 Risk factors *a priori* accessible to corrective treatment

4.2.1.2.1 It is recommended to the length of pre-operative hospitalization be less than 4 days.

4.2.1.2.2 It is recommended that tobacco abuse be completely interrupted 6 to 8 weeks before placement of a hip or knee prosthesis.

4.2.1.2.3 It is recommended to prevent obesity and denutrition even though there is no published data demonstrating its adequacy.

4.2.1.2.4 Diabetes is an acknowledged risk factor for SSI, it is recommended to perform revascularization surgery in case of arterial disease and to normalize peri-operative glycemia by using insulinotherapy IV if necessary.

4.2.1.2.5 It is recommended to take into account rheumatoid polyarthritis and other inflammatory rheumatoid treatments as mentioned in paragraph **1.2**

4.2.1.2.6 It is not recommended to screen systematically for carriage of methicillin susceptible *Staphylococcus aureus* for its pre-operative eradication whatever the type of surgery. When *Staphylococcus aureus* SSI rates remain unusually high (superior to 2%), it is recommended to perform nasal swabs of caregivers and pre-operative nasal swabs of patients. In this case, mupirocin treatment is recommended. Nasal screening for methicillin resistant *Staphylococcus aureus* (MRSA) is recommended in patients who must undergo planned cardiac or orthopedic surgery, transferred from ICU, long and median stay structure, or in case of chronic cutaneous lesions. It is not recommended to use mupirocin systematically pour to prevent the onset of SSI in MRSA carriers. American 2008 SHEA and IDSA recommendations on the prevention of SSI classify screening and decolonization of nasal *Staphylococcus aureus* carriage in non-solved points.

4.2.1.2.7 It is advised to use the general recommendations made for surgery in case of carriage of other multi-resistant bacteria.

4.2.1.2.8 It is recommended to screen for any infection at distance of the operative site and to treat it.

4.2.1.2.9 It is recommended to screen for any infection away from the operative site and to treat it outside of any surgical context, in every patient with a prosthesis or osteosynthesis material.

4.2.2 Global prevention measures against infection in orthopedic and trauma surgery

1. Recommendations for *skin care and preparation* were specified in the consensus conference «pre-operative management of infectious risk».

2. *Systemic route antibioprophylaxis* was codified by the 1992 consensus conference «antibioprophylaxis in surgical settings in the adult», and updated in 1999.
3. It is recommended to use local antibiotherapy for prophylaxis such as antibiotic impregnated cements for first intention arthroplasty.
4. *Per-operative apyrexia* is applicable to orthopedic and traumatological surgery.
5. *Peri-operative hyperoxygenation* could be used for orthopedic and traumatological surgery.

4.3 What measures are undertaken to fight the risk of cross transmission when managing a patient infected in an orthopedic surgical block?

4.3.1 Should there be a chronological order for surgery?

There is no need to impose a specific order of passage in hygiene precautions are observed **(grade C).**

4.3.2 What precautions should be taken in the surgical block after operating a septic patient?

It is recommended to perform the usual cleaning program and to respect the time needed for particle decontamination of the operating room between two interventions. In case of MRB, there are no supplementary precautions to take for the cleaning of the rooms but complementary precautions of the «contact» type must be respected during care giving **(grade C).**
The idea of «septic» operating room has sometimes been supported. But there are no studies or consensus to prove the superiority of this organization concerning the succession of surgeries with various contamination classes in the same operating room if cleaning procedures between two interventions are observed and the rooms are equipped with efficient ventilation systems **(level 3).**
There is no need to have separate post surgery surveillance rooms for patients having undergone different surgeries, and especially clean surgery (Altemeier class I) and contamination class II, III, or IV surgery. Nevertheless, patients at high-risk of developing an infection and those undergoing contamination class I surgery should be grouped and roomed apart from patients having undergone surgery classified II or higher.

Question 5: what compensation for the consequences of post-operative prosthetic device infections?

5.1 What should be attributed to care and how avoidable are these prosthetic device bone and joint infections?

It is recommended to consider as usually associated to care bone and joint infections of the operative site occurring in the year after surgery for placement of an implant, a prosthesis, or prosthetic material.

Nevertheless, and whatever the delay of onset, it is recommended to assess for every case the possibility of a link between surgery and infection, especially by taking into account the causative pathogen.

It is recommended to assess the preventability of bone and joint infection on material associated to healthcare, case-by-case and *a posteriori*. The presence of an underlying physiological or pathological state, the endogenous or exogenous aspect of the causative germ, observance of rules for care-giving at the time of onset of the adverse event (preventive and curative for the infection), and the institution's observance of regulations concerning the prevention of nosocomial diseases should be taken into account and analyzed.

It is recommended to assess the imputation of bone and joint infection on material associated to healthcare medically by identifying the plausibility of the causal link according to the site of infection and its anatomic proximity with the invasive procedure (superficial infection of the operative site or deep infection concerning the bone in that case), the association to a space and time context compatible with the length of infection incubation (delay between the intervention and the diagnosis infection of 1 year or more), the causative germ's ecology (often endogenous due to cutaneous flora). It is also necessary to determine if the onset of infection is abnormal when considering the patient's anterior state (physiological or pathological) and its forecasted evolution and to rule out any other cause.

Patient's medical file

According to current legislation, the medical file of a patient undergoing bone and joint surgery with material must include consultation reports, the patient's consent, skin preparation, anesthesia file including the antibioprophylaxis protocol and the traceability of its administration, surgical report, results of microbiological sampling, the complete nursing care report, medical and paramedical prescriptions.

Other elements allowing to assess the quality of the institution's organization for the prevention of nosocomial infections must be available: proof of instrument sterilization, traceability of the patient's implants and skin preparation, documents concerning the preparation and biocleaning of the operating room, maintenance protocols for the material, Committee for the prevention of nosocomial infections (CLIN) reports on hygiene protocols, their validation, the monitoring of des nosocomial infections, of hospital environment, report of infection cases in the unit during the contemporary period, etc.
It is recommended to support the development of computerized medical files with powerful and secure software, to help with teamwork.

5.2 What information should be given to patients? Before surgery, during hospitalization, in case of infection?

It is recommended to give the patient understandable information before bone and joint surgery with implantation of material on:

- his disease, the diagnosis, and the various alternative therapies;
- the exact nature of surgery and its possible consequences, especially infectious;
- the benefits and les risks of the various alternative therapies,
- the circumstances and causes of damage, its potential consequences and therapeutic modalities in case of a healthcare related infection.

It is recommended that practitioners develop in their everyday activity the use of tools allowing to trace all elements of the medical file.

What are the possibilities for compensation of prosthetic device bone and joint infections?

It is recommended to for the medico legal assessment of bone and joint infections on material, that reports be made by experts with required competences in orthopedics, microbiology, infectiology, hospital hygiene so as to make sure that the management was made adequately in agreement with the current «guidelines», respect of rules specific to each type of jurisdiction and a detailed description of the various domains of prejudice.

ADDENDUM 1: Gustilo classification

Grade I

Skin puncture without delamination

- wound less than 1 cm w/ minimal soft tissue injury
- wound bed is clean
- bone injury is simple w/ minimal comminution

Grade II

- Linear wound > 1 cm
- Skin delamination

wound is greater than 1 cm w/ moderate soft tissue injury
- wound bed is moderately contaminated;
- fracture contains moderate comminution

Grade III

- Extensive soft tissue and nerve injury
- Comminutive fractures
- Loss of bone substance

- **III A** = soft tissue coverage of bone is usually possible
- **III B** = soft tissue coverage impossible
  Loss of bone substance
- **III C** = Fracture associated to arterial trauma

ADDENDUM 2: definition of sepsis, severe sepsis, and septic shock

Sepsis

It is the association of a systemic inflammatory response, including:

- body temperature > 38 °C or < 36 °C
- cardiac rhythm > 90 b/p/min
- respiratory rhythm > 20/p/min
- leucocytes > 12,000/mm3 or < 4,000/mm3

with an infection at least clinically diagnoses.

Severe sepsis

It is a sepsis associated to an organ dysfunction (hypoxemia, urinary stream < 0.5 ml/kg/h, coagulation disorder, metabolic acidosis), hypo-perfusion (lactic acidosis, oliguria, acute encephalopathy), or hypotension.

Septic shock

It is a sepsis associated to a persistent hypotension, despite a qualitatively and quantitatively adapted vascular filling, accompanied or not with signs of hypo-perfusion.

ADDENDUM 3: Checketts-Otterburns classification

Grade 1

- Slight redness
- Little discharge

Grade 2

- Redness of skin
- Discharge
- Pain

Grade 3

- Grade 2 not improved with antibiotics

Grade 4

- Severe soft tissue infection involving several pins with associated loosening of pins

Grade 5

- Grade 4 with bone infection visible on radiographs

Grade 6

- Infection occurring after removal of the external fixator (pathway of a previous pin) visible on X-ray (sequestra)

The **first 3 grades** correspond to minor infections for which the infected pin may be left in place; the **last 3 grades** correspond to major infections requiring the removal of the infected pin.