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ORIGINAL RESEARCH

High Frequency of Polymicrobial Infections After Surgical Resection of Malignant Bone and Soft Tissue Tumors: A Retrospective Cohort Study

Laura M. Vos · Philippe C. Morand · David Biau · Denis Archambeau · Luc-Jean Eyrolle · Julien Loubinoux · Valerie Perut · Philippe Leclerc · Joop E. Arends · Philippe Anract · Dominique Salmon

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ABSTRACT

Introduction: Surgical resection of a malignant bone tumor (BT) or soft tissue tumor (STT), with or without prosthetic replacement, carries a high risk of developing postoperative infections. There is limited knowledge on the bacteriological spectrum of these postsurgical infections that necessitate empirical antibiotic therapy. The aim of this study was to analyze the incidence and microbiological features of site infections following BT or STT resection.

Methods: In this retrospective mono-center study, we analyzed the surgical and bacteriological data of all consecutive patients who developed an infection after surgical resection of a BT or STT between January 2010 and April 2014.

Results: Seventy-two consecutive patients who developed an infection on the site of surgical treatment for a BT ($n = 42$) or SST ($n = 30$) were included. Polymicrobism was frequently observed, more often associated with STTs (93%) than BTs (71%; $P = 0.03$).

L. M. Vos · D. Salmon
Infectious and Tropical Medicine, Internal Medicine Department, Cochin Hospital APHP, Paris, France

D. Salmon
e-mail: dominique.salmon@cch.aphp.fr

L. M. Vos · J. E. Arends (✉)
Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, The Netherlands
e-mail: J.E.Arends@umcutrecht.nl

P. C. Morand · J. Loubinoux
Bacteriology Department, Cochin Hospital APHP, Paris, France

P. C. Morand · D. Biau · J. Loubinoux · P. Anract · D. Salmon
Université Paris Descartes, Sorbonne Paris Cité, Paris, France

D. Biau · P. Leclerc
Orthopedic Surgery Department, Cochin Hospital APHP, Paris, France

D. Archambeau · L.-J. Eyrolle
Department of Anesthesiology, Cochin Hospital APHP, Paris, France

V. Perut
Department of Public Health, Cochin Hospital APHP, Paris, France

P. Anract
Orthopedic Department, Cochin Hospital APHP, Paris Descartes University, Paris, France
e-mail: Philippe.anract@aphp.fr

Gram-negative bacteria were more frequently isolated in STTs (55%) than in BTs (26%; $P = 0.01$) and non-prosthesis-associated infections (54%) than prosthesis-associated infections (29%; $P = 0.04$), whereas staphylococci were more frequently found in BTs (76%) than in STTs (52%; $P = 0.03$). Overall, we found gram negatives in 82% of early acute infections, 11% of chronic infections and 7% of late acute infections ($P < 0.01$).

Conclusion: Postoperative infections in patients after surgical resection of BTs or STTs were often polymicrobial, especially following STTs. Causative bacteria were often gram negatives in STTs and non-prosthesis-associated infections, whereas staphylococci were predominant in BTs. Based on these findings, we recommend antibiotic coverage of both gram-positive and -negative bacteria with a combination of broad-spectrum antibiotics in STTs and antistaphylococcal antibiotics as first-line therapy in infections following BT surgery.

Keywords: Bone tumor; Infection postsurgical resection; Microbiology; Soft tissue tumor

INTRODUCTION

Patients undergoing surgical resection for a malignant bone tumor (BT) or soft tissue tumor (STT), e.g., sarcomas, are at high risk for infectious complications [1]. A recent meta-analysis of 48 studies involving 4838 patients who underwent surgery for malignant BTs of the lower extremities showed a postoperative infection rate of 10% [2]. Similar postoperative infection rates of around 10% were reported in STT patients [3]. A longer duration of surgery, invalidating surgery, impaired systemic or local immunosuppressive state due to chemotherapy or adjuvant radiation, poor general performance status and implanted material left at the operative site may decrease host defenses, leading to infection [4, 5]. Postsurgical infections can lead to reoperation with frequent need for prosthesis removal [6] in combination with antibiotic treatment, decreased function of the extremity and increased pain resulting in incremental healthcare costs [3, 7, 8].

In the absence of renewed surgical intervention, antibiotic therapy for postsurgical infections shows success rates lower than 10% [1]. One of the reasons for this low success rate is the lack of data concerning the microbiological spectrum of infections following surgery for BTs and STTs. First, isolation and identification of all causing bacteria are time consuming and not always successful [6]. Furthermore, there are hardly any large studies performed in patients with postsurgical infections after resection of a BT or STT. This results in limited data to guide first-line antibiotic therapy. The optimal way, e.g., the gold standard, to establish the microbiological spectrum of a postoperative infection is to obtain peroperative cultures from the surgical site of a postsurgical infection. Postsurgical infections following resections of BTs and STTs are associated with high patient morbidity, and therefore precise microbiological data are needed for better empiric antibiotic therapy.

This study aimed at evaluating the bacteriological spectrum of malignant BT- and STT-associated postsurgical infections in order to improve the effectiveness of antibiotic treatment, thereby decreasing patient morbidity. We show that different causative agents observed for either BT or STT postsurgical infections are involved and that this knowledge could help clinicians to redefine more specific empirical antibiotic treatments in both cases.

METHODS

Study Design

We performed a retrospective observational monocenter study of all consecutive adult patients who had a surgical resection in the orthopedic department of a malignant primary or secondary BT, or a malignant STT, presenting with a postsurgical infection between 1 May 2010 and 1 April 2014 at the Cochin Hospital (Paris Descartes University, Paris, France). Cochin Hospital is a tertiary referral center for BTs and STTs with a separate infectious diseases ward within the orthopedic department. The treatment of all patients is discussed weekly in a multidisciplinary infection meeting (MDIM) attended by orthopedic surgeons, anesthesiologists, medical microbiologists, infectious disease physicians and pharmacists. All procedures followed were in accordance with the ethical standards.

Inclusion Criteria

Inclusion criteria were (1) histologically confirmed diagnosis of a malignant primary or secondary BT or a malignant STT, (2) surgical treatment for the tumor (tumor resection whether or not followed by reconstruction), (3) age above 15 years at the time of infection and (4) at least one postsurgical infection at the resection site confirmed by the treating staff. Since only cultures of peroperative samples were considered as relevant for microbiological documentation, patients were excluded if they did not get surgical treatment for their infection. Patients who underwent surgery more than once during infection treatment were included only once. Visceral mesenchymal tumors were excluded.

Data Collection

The following data were collected from the medical records: (1) age, (2) sex, (3) body mass index (BMI, kg/m^2), (4) American Society of Anesthesiologists (ASA) score at the time of infection, (5) tumor histology, (6) details of surgical and nonsurgical treatments (e.g., chemotherapy and radiotherapy) for the tumor, (7) bacteriological documentation before and at the time of surgical interventions for all (re)infection(s), and (8) surgical and antibiotic treatment of the (re)infection(s). For most patients, data on peroperative antibiotic prophylaxis were not properly documented and were therefore not collected.

Histological data confirming the diagnosis of malignant tumor, including the type of tumor, localization and grade, were retrieved from either pre- or peroperative histological material, anesthesiological files or external documentation. Bacteriological data, e.g., bacteria and antibiotic resistance patterns, were collected from pre-, per- or postoperative biological samples, blood or any suspected port of entry. Medical treatment data were collected for both tumors and infections. For tumors, the types of surgical intervention and treatments with pre- or postoperative chemo- or radiotherapy were retrieved from all surgical operation reports. For the (re)infections, the type of surgical intervention was noted. Postoperative antibiotic treatment for infection was evaluated for theoretical effectiveness using the antibiotic susceptibility testing pattern of the bacterial isolates that were considered as causative pathogens, e.g., isolated from pre- or peroperative specimens. The mono- or polymicrobism was analyzed, as well as the incidence of different pathogens gathered in different categories.

Methods for Bacteriological Isolation and Antibiotic Susceptibility Testing

Peroperative samples were homogenized before streaking onto two sets of horse blood and heated blood agar (BioMerieux, France) and incubated under aerobic or anaerobic conditions at 35 °C. One agar set was observed up to 48-h incubation, and the second set was left untouched until examination at day 7. A Schaedler enrichment broth (BioMerieux, France) was also inoculated and examined daily up to 14 days. Bacterial isolates of interest were identified using MALDI TOF (MALDI BioTypr, BrukerDaltonik, Germany), and antibiotic susceptibility testing was conducted by disc diffusion method in accordance with EUCAST 2013 guidelines. When available, rectal carriage of extended-spectrum beta-lactamase (ESBL) and nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) at the time of infection were retrieved from the bacteriological files.

Definitions

Tumors were subdivided into malignant primary and secondary BTs or malignant STTs. Oncologic surgical treatments were subdivided based on type of surgery: tumor resection or limb amputation (e.g., non-prosthetic) or tumor resection with prosthesis implantation, including osteosynthesis and/or allograft implantation. Localization was subdivided into (1) the upper limb from the shoulder joint to hand, (2) ribs and/or spine, (3) pelvis, including the sacrum and tumors in both the pelvis and hip, and (4) lower limb from the hip joint to foot, including tumors in both the leg and hip. The oncologic grade of the tumors was subdivided into 1, 2 or 3 (French FNCLCC grading system) for STTs and a low or high grade (Enneking grading system) for BTs.

The diagnosis of infection was derived from consensus by the MDIM, based on the clinical presentation and inflammatory signs (e.g., general signs such as fever, malaise and local symptoms such as pain, redness, swelling, hardness and fluid leakage from surgical scars), operation reports and laboratory findings [blood C-reactive protein (CRP), abundance of leukocytes in peroperative samples). A distinction was made between osteomyelitis (bone infection) and erysipelas/cellulitis (soft tissue infection) at the time of the MDIM based on surgical, radiological and clinical evidence for osteitis. Infection was categorized as early acute (<1 month postresection), late acute (1–3 months postoperative) or chronic (>3 months postoperative).

All infections were first treated surgically, and antibiotic treatment was started peroperatively as soon as clinical samples had been obtained, with a recommended duration of 6–12 weeks (osteomyelitis) or 21 days (cellulitis). Surgical treatments for infection were subdivided according to surgery type. Antibiotic therapy given for postoperative surgical site infections was subdivided in (1) monotherapy for each bacterial isolate, (2) combination therapy for all isolated bacteria, (3) the antibiotic spectrum not covering all infectious bacteria, (4) probabilistic antibiotic therapy with negative microbiological cultures or (5) no antibiotic therapy.

Statistical Analysis

We performed a descriptive analysis of clinical and bacteriological data. The primary endpoint of this study was the difference in causative bacteriological pathogens of postsurgical infections between BTs and STTs. Secondary

endpoints were differences in causative bacteriological pathogens among (1) three different types of infection (osteomyelitis, cellulitis or both), (2) four different localizations (upper limbs, vertebrae, pelvis or lower limbs) and (3) prosthesis or non-prosthesis-associated infections combined with nonsurgical tumor treatments, e.g., chemo- or radiotherapy pre- or postoperatively. Continuous variables were expressed as medians with interquartile range (IQR; Q1–Q3), whereas categorical variables were noted as numbers with percentages (%). We used the t test or one-way analysis of variance test for continuous variables with a normal distribution and a χ^2 test or Fisher exact test (*) for categorical variables. A two-sided P value of <0.05 was considered statistically significant. Person-years of follow-up for each patient were computed as the time from the index date (date of first presentation with infection at the hospital) to the end of follow-up (1 April 2014), death or loss to follow-up. Statistical analysis was performed using SPSS software, version 22 (IBM SPSS, Chicago, IL, USA).

RESULTS

Patient Characteristics

Seventy-two consecutive patients who developed a postsurgical infection after resection of a BT ($n = 42$) or STT ($n = 30$) were included (Fig. 1). The study population is detailed in Table 1 and consisted of 34 males and 38 females with a mean age of 49.8 years (SD ± 19.2) and a mean BMI of 25.7 kg/m^2 (SD ± 5.1).

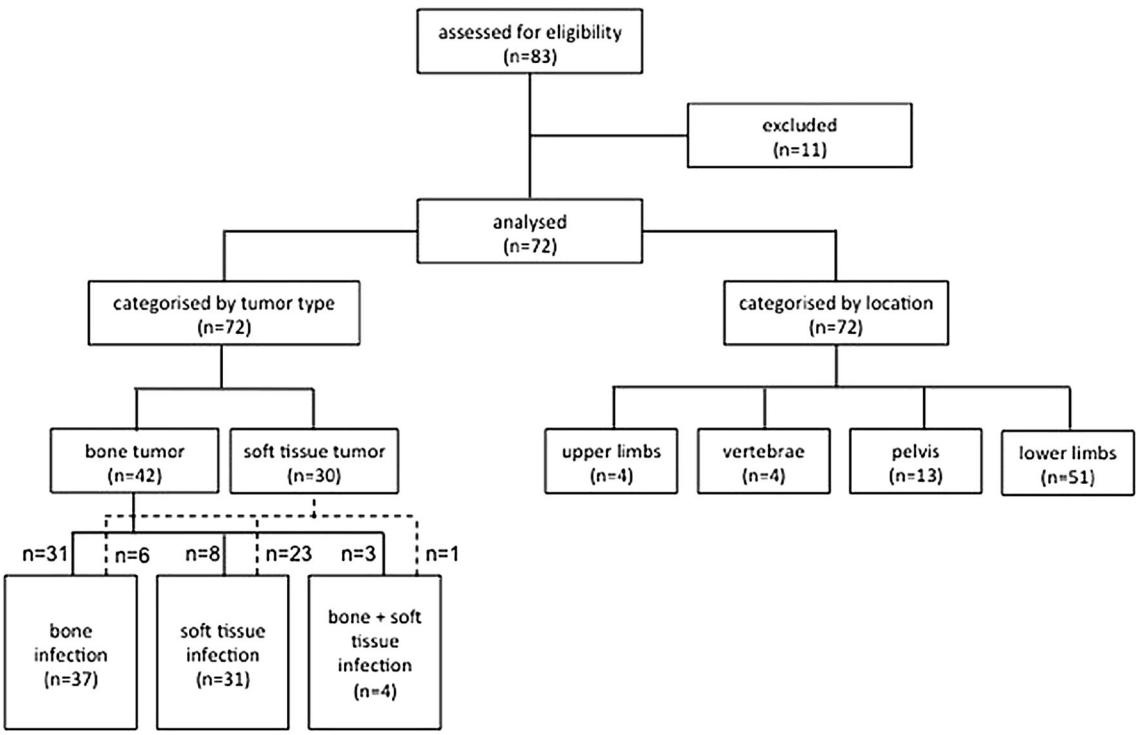

Fig. 1 Flowchart inclusion of the 72 patients who had a postoperative site infection after surgery for a BT or STT

Table 1 Baseline characteristics of 72 patients with an infection following surgical treatment of a BT or STT

Characteristics	All patients ($N = 72$)	BT ($N = 42$)	STT ($N = 30$)	*P* value
Sex, male	34 (47.2)	24 (57.1)	10 (33.3)	**0.046**
Age at time of infection, years (mean ± SD)	49.8 ± 19.2	44.6 ± 17.4	57.1 ± 19.5	**0.006**
BMI, kg/m^2 (mean ± SD)	$N = 69$	$N = 41$	$N = 28$	0.811
	25.7 ± 5.1	25.9 ± 5.8	25.6 ± 3.8	
ASA ≥3	22 (30.6)	12 (28.6)	10 (33.3)	0.665
MRSA carriage	$N = 42$	$N = 29$	$N = 13$	0.528*
	2 (4.8)	1 (3.4)	1 (7.7)	
ESBL carriage	$N = 37$	$N = 26$	$N = 11$	0.205*
	3 (8.1)	1 (3.8)	2 (18.2)	
Localization of tumor				
Upper limb	4 (5.6)	3 (7.1)	1 (3.3)	0.636*
Vertebrae or ribs	4 (5.6)	4 (9.5)	0	0.135*
Pelvis[a]	13 (18.1)	9 (21.4)	4 (13.3)	0.379
Lower limb[b]	51 (70.8)	26 (61.9)	25 (83.3)	**0.049**
High grade[c] of primary tumor	28 (66.7)	9 (52.9)	19 (76)	0.120
Nonsurgical treatment for tumor				
Chemotherapy	29 (40.3)	19 (45.2)	10 (33.3)	0.310
Radiotherapy	21 (29.2)	5 (11.9)	16 (53.3)	**0.000**
Type of infection				
Bone infection[d]	37 (51.4)	31 (73.8)	6 (20)	**0.000**
Soft tissue infection[d]	31 (43.1)	8 (19)	23 (76.7)	**0.000**
Bone and soft tissue infection[d]	4 (5.6)	3 (7.1)	1 (3.3)	0.636*
Last tumor operation—infection, days (mean ± SD)	186 ± 787	278 ± 1023	56 ± 88	0.240
Onset and duration of symptoms				0.811
Early acute infection[e]	40 (55.6)	22 (52.4)	18 (60)	
Late acute infection[e]	19 (26.4)	12 (28.6)	7 (23.3)	
Chronic infection[e]	13 (18.1)	8 (19)	5 (16.7)	
Infection management				
Surgery for (re)infection(s), *n* (mean ± SD)	1.8 ± 1.1	1.9 ± 1.1	1.7 ± 1.0	0.420
>1 surgical operation for infection	36 (50)	22 (52.4)	14 (46.7)	0.633
AB after first surgery for infection	68 (94.4)	40 (95.2)	28 (93.3)	1.000*
AB monotherapy for ≥1 causative agent	27 (39.7)	8 (20)	19 (67.9)	**0.000**

Table 1 continued

Characteristics	All patients ($N = 72$)	BT ($N = 42$)	STT ($N = 30$)	P value
AB combitherapy against all causative agents	36 (52.9)	28 (70)	8 (28.6)	**0.001**
AB suppressive therapy	5 (6.9)	4 (9.5)	1 (3.3)	0.393*

Values are presented as n (%) unless otherwise stated

Bold indicates significant P values

Histology of tumors: primary BTs included: osteosarcomas ($n = 18$), chondrosarcomas ($n = 5$), Ewing tumors ($n = 2$), chordomas ($n = 3$), giant cell tumors ($n = 2$), adamantinomas ($n = 2$) and undifferentiated BTs ($n = 1$). Secondary BTs ($n = 9$) were all metastatic adenocarcinoma. STTs ($n = 30$) included: synovialosarcomas ($n = 2$), (myxo)fibrosarcomas ($n = 7$), leiomyosarcomas ($n = 4$), liposarcomas ($n = 7$), rhabdomyosarcomas ($n = 1$) or undifferentiated STTs ($n = 9$)

AB antibiotic, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *BT* bone tumor, *ESBL* extended-spectrum beta-lactamase, *MRSA* methicillin-resistant *Staphylococcus aureus*, *STT* soft tissue tumor

* Fisher's exact test. If no *, an χ^2 test was used

[a] Including tumors in the hip or pelvis

[b] Including tumors in the hip or leg

[c] French FNCLCC grading system (high grade = grade 3) for soft tissue tumors and Enneking grading system (high grade = grade 2) for bone tumors

[d] Bone infection = treated with antibiotics for ≥4 weeks; soft tissue infection = treated with antibiotics for 2 days–3 weeks; both = treated with antibiotics at least once for 6 weeks and at least once for 2 weeks

[e] Early <1 month, late >1 month after last surgery for tumor

Histological Features and Treatments for Tumor

BTs ($n = 42$) consisted of primary BTs (79%) and secondary BTs (21%). Histological and oncological characteristics of the tumors are presented in Table 1. Surgical treatment involved tumor resection with limb salvage in 96% and amputation in 4% (BTs 0%, STTs 10%; $P = 0.07$). Reconstruction involved a prosthesis in 36% (BTs 57%, STTs 7%; $P < 0.01$) and allograft and/or osteosynthesis in 26% (BTs 29%, STTs 23%; $P = 0.60$). Chemotherapy following tumor resection was more frequent in the upper limb (BTs 50%, STTs 0%) and vertebral tumors (BTs 50%, STTs 0%) than in pelvic (0%) and lower limb tumors (BTs 23%, STTs 20%; $P = 0.03$). Preoperative radiotherapy was performed significantly more often in patients with subsequent cellulitis (39%) than in those with osteomyelitis (16%; $P = 0.04$).

Clinical Characteristics of the Infections

Infection characteristics are shown in Table 1. The median duration between the last oncological operation and first infectious episode was 28 days (IQR 13–72 days). Infections were considered as early acute (<1 month) in 40 patients (56%), late acute (1–3 months) in 19 (26%) and chronic (>3 months) in 13 (18%). Thirty-seven (51%) patients were diagnosed with osteomyelitis (31 BT patients, 6 STT patients), 31 (43%) with cellulitis (8 BT patients, 23 STT patients) and 4 (5%) with both (3 BT patients, 1 STT patient; Fig. 1). In 68 patients (94%), the causative pathogen was obtained by culture, whereas no causative pathogen was identified in the remaining four patients, despite clinical and histological evidence for infection at revision surgery. Blood cultures were available for 30 patients, of whom 6 (20%) had a bacteremia with the same pathogen as found at the surgical site.

Table 2 Bacteriological documentation of the 72 infections in patients surgically treated for a BT or STT

Bacteria in first intervention	All patients ($N = 71$)	BT ($N = 42$)	STT ($N = 29$)	P value
Causing organisms at first intervention				
Patients with positive culture	68 (95.8)	40 (95.2)	28 (96.6)	1.000*
Patients with gram-positive species	62 (87.3)	37 (88.1)	25 (86.2)	1.000*
Patients with gram-negative species	27 (38)	11 (26.2)	16 (55.2)	**0.013**
Patients with anaerobic species	15 (21.1)	6 (14.3)	9 (31)	0.089
Polymicrobism	44 (62)	30 (71.4)	27 (93.1)	**0.032**
Number of species, *n* (mean ± SD)	2.38 ± 1.57	2.00 ± 1.53	2.93 ± 1.49	**0.013**
Staphylococci	47 (66.2)	32 (76.2)	15 (51.7)	**0.032**
MSSA	24 (33.8)	16 (38.1)	8 (27.6)	0.357
MRSA	0	0	0	–
MSCNS[a]	18 (25.4)	12 (28.6)	6 (20.7)	0.453
MRCNS[b]	14 (19.7)	11 (26.2)	3 (10.3)	0.099
Streptococci	12 (16.9)	4 (9.5)	8 (27.6)	**0.059***
S. pneumoniae	1 (1.4)	0	1 (3.4)	0.408*
S. agalactiae/*S. dysgalactiae*	5 (7)	2 (4.8)	3 (10.3)	0.393*
Other streptococci[c]	6 (8.5)	2 (4.8)	4 (13.8)	0.218*
Other gram-positive species	25 (35.2)	8 (19)	17 (58.6)	**0.001**
Enterococci[d]	23 (32.4)	8 (19)	15 (51.7)	**0.004**
Other gram-positives[e]	3 (4.2)	0	3 (10.3)	0.064*
Gram negatives	27 (38)	11 (26.2)	16 (55.2)	**0.013**
Non-ESBL Enterobacteriaceae[f]	25 (35.2)	10 (23.8)	15 (51.7)	**0.015**
P. aeruginosa[g]	5 (7)	3 (7.1)	2 (6.9)	1.000*
Other gram negatives[h]	3 (4.2)	1 (2.4)	2 (6.9)	0.563*
Anaerobes	15 (21.1)	6 (14.3)	9 (31)	0.089
P. acnes[i]	4 (5.6)	4 (9.5)	0	0.140*
Other anaerobic species[j]	11 (15.5)	2 (4.8)	9 (31)	**0.005***

Values are presented as *n* (%) unless otherwise stated

Bold indicates significant *P* values

BT bone tumor, *ESBL* extended-spectrum beta-lactamase, *MRCNS* methicillin-resistant coagulase-negative staphylococcus, MRSA methicillin-resistant *S. aureus*, *MSCNS* methicillin-susceptible coagulase-negative staphylococcus, *MSSA* methicillin-susceptible *S. aureus*, *P. acnes Proprionibacterium acnes*, *P. aeruginosa Pseudomonas aeruginosa*, *S. agalactiae Streptococcus agalactiae*, *S. dysgalactiae Streptococcus dysgalactiae*, *S. pneumoniae Streptococcus pneumonia*, *STT* Soft tissue tumor

* Fisher's exact test (χ^2 test was used in other cases)

[a] *Staphylococcus epidermidis*, *Staphylococcus capitis*, *Staphylococcus warnerii*, *Staphylococcus haemolyticus*, *Staphylococcus caprae*, *Staphylococcus pasteuri*, *Staphylococcus lugdunensis*, *Staphylococcus hominis*

[b] *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus capitis*, *Staphylococcus hominis*

[c] Streptococci or related: *Streptococcus anginosus*, *Streptococcus sangnuinis*, *Streptococcus oralis*, *Streptococcus constellatus*, *Streptococcus salivarius*, *Granulicatella adiacens*, *Helcococcus* sp., *Gemella* morbillorum

[d] *Enterococcus faecium*, *Enterococcus faecalis*, *Enterococcus durans*, *Enterococcus raffinosus*

[e] *Dermabacter hominis*, *Corynebacterium* spp. (*C. jeikeium*, *C. amycolatum*, *C. ramosum*, *C. perfringens*, *C. simulans*, *C. tuberculostearicum*), *Actinobaculum schaalii*

[f] *Escherichia coli*, *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Proteus mirabilis*, *Morganella morganii*, *Cronobacter sakazakii*, *Leclercia adecarboxylata*, *Citrobacter amalonaticus*

[g] And *Pseudomonas stutzerii* (1 patient)

[h] *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*

[i] And *Proprionibacterium avidum*

[j] *Bacteriodes fragilis*, *Bacteriodes ovatus*, *Finegoldia magna*, *Prevotella intermedia*, *Peptoniphilus harei*, *Actinomyces odontolyticus*, *A. turicensis*, *Parvimonas micra*

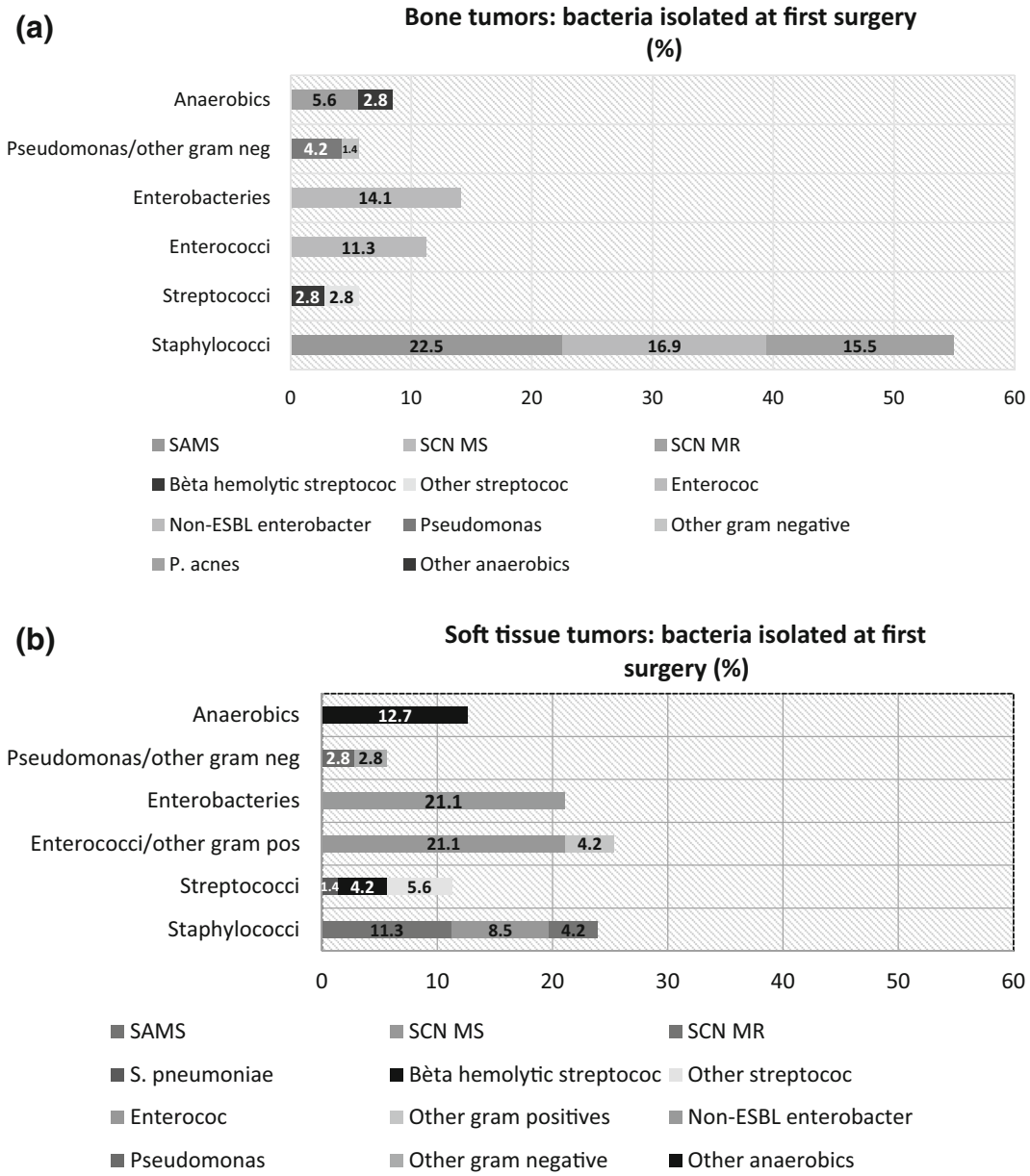

Fig. 2 Incidence of bacteria in pre-, per- and postoperative samples of the first intervention for infection. Groups of species are shown as percentages of the total number of bacteria isolated from the first surgery ($n = 142$, 71 in BT and 71 in STT) in 71 patients from whom samples were retrievable. *Betahaemolytic streptococci* = *Streptococcus agalactiae/Streptococcus dysgalactiae*. Pseudomonas = *P. aeruginosa* and *P. stutzeri*. *ESBL* Extended-spectrum beta-lactamase, *SAMS Staphylococcus aureus* methicillin-susceptible, *SCN MR* Staphylococcus coagulase-negative methicillin-resistant, *SCN MS* Staphylococcus coagulase-negative methicillin-susceptible

Microbiological Features

Microbiological findings associated with postsurgical infections after resection of BTs and STTs are presented in Table 2 and Fig. 2. Forty-four patients (62%) had a polymicrobial infections. Polymicrobial infection occurred more frequently in STTs than in BTs (93% vs.

71%; $P = 0.03$) and likewise in cellulitis versus osteomyelitis patients (77% vs. 51%; $P = 0.01$; Fig. 1). Localization was not linked with the number of causative pathogens, nor was the timing of infection (i.e., early acute, late acute or chronic).

Staphylococci as a group were significantly more predominant in BTs than in STTs (76% vs. 52%; $P = 0.03$). *S. aureus* was present in 38% of BTs and 28% of STTs ($P = 0.36$) and coagulase-negative staphylococci (CNS) in 50% of BTs and 28% of STTs ($P = 0.06$). Other gram-positive bacteria were significantly more frequent in STTs than in BTs (86% vs. 29%; $P < 0.01$), among which enterococci (52% vs. 19%; $P < 0.01$) and streptococci (28% vs. 10%; $P = 0.06$) were predominant. Gram-negative bacteria were also significantly more frequent in STTs than in BTs (55% vs. 26%; $P = 0.01$), among which non-ESBL Enterobacteriaceae (24% vs. 52%; $P = 0.02$) and *Pseudomonas aeruginosa* (7% vs. 7%; $P = 1.00$) were most frequent.

We compared the microbial spectrum between prosthesis-associated infections (including patients' allografts and osteosynthesis material) and non-prosthesis-associated infections. We found that gram-negative bacteria occurred more frequently in postoperative infections without prosthesis material, 54% vs. 29% ($P = 0.04$). Enterococci were more frequent in non-prosthesis-associated infections, 67% vs. 11% ($P < 0.01$). Furthermore, the number of cultured bacteria was less in prosthesis-associated infections, with a mean 4.19 ± 2.56 bacteria in non-prosthesis infections and 2.96 ± 1.83 in prosthesis-associated infections ($P = 0.05$). We also subdivided BT and STT patients and compared their microbiological spectrum according to tumor treatment, e.g., resection and/or prosthesis in combination with additional chemo- or radiotherapy. In non-prosthesis-associated infections with or without additional chemo- or radiotherapy in BT patients, we found more frequent gram-negative bacteria (67% vs. 19%; $P = 0.03$), Enterococci (67% vs. 11%, $P < 0.01$), Enterobacteriaceae (67% vs. 17%; $P = 0.02$) and anaerobes (33% vs. 0%; $P = 0.02$). For STT patients no significant differences were found in the microbiological spectrum when comparing tumor treatment groups.

When comparing cellulitis and osteomyelitis infection irrespective of underlying malignancy, no significant differences were seen in the distribution of gram positives and gram negatives. However, anaerobes were more frequently isolated from cellulitis (30%) than from osteomyelitis (5.4%; $P = 0.03$).

Localization did not significantly affect the scope of causative pathogens, except for *Proprionibacterium acnes*, which was more frequent in the upper limbs compared to the vertebrae, pelvis and lower limbs ($P = 0.02$).

For BTs and STTs together, we found gram negatives in 82% of early acute infections, in 7% of late acute infections and in 11% of chronic infections ($P < 0.01$).

Treatments for Infection

Surgery was followed by antibiotic treatment for almost all patients (99%). Thirty-six patients (50%) had one surgical intervention and 36 (50%) had more than one.

The median duration of antibiotic treatment was 3.7 weeks (IQR 5 weeks), with a median of 4.4 weeks for BT patients (IQR 4 weeks) and 2.3 weeks for STT patients (IQR 2 weeks; $P = 0.08$). Antibiotic therapy duration $\geq$6 weeks was more frequently associated with successful clinical outcome in BTs (and osteomyelitis) than a shorter duration

(<6 weeks) of antibiotic therapy (53% vs. 16%; $P = 0.02$). In STTs and cellulitis, no significant difference in clinical outcome was seen between a longer (≥3 weeks) or shorter (<3 weeks) duration of antibiotic therapy (57% vs. 29%; $P = 0.36$). Five (7%) patients received lifelong suppressive antibiotics as an alternative to further surgical treatment, either after the first surgery ($n = 3$) or one of the following surgeries ($n = 2$).

Antibiotic choice was made by clinicians and was confirmed through MDIM. Thirty-five different molecules were used. The most frequently used antibiotics as initial monotherapy or combination therapy were the following: piperacillin-tazobactam (13%), amoxicillin/clavulanic acid (10%), gentamicin (9%), pefloxacin (9%) or vancomycin (9%). Thirty-one percent of initial antibiotherapies were switched to a second line mono- or combination antibiotherapy, involving gentamicin (60%), vancomycin (48%), amoxicillin/clavulanic acid (25%), pefloxacin (17%) and tazobactam (15%).

DISCUSSION

We studied the microbiological spectrum of infections following surgical resection of BTs and orthopedic STTs in a relatively large number of patients, presenting the largest patient group of postoperatively infected STTs patients ($n = 30$) to our knowledge.

First, we show that postoperative infections in STTs are polymicrobial in 88% of the cases, whereas post-BT infections are more frequently monomicrobial, involving mainly staphylococci. Several reasons can be hypothesized for polymicrobism in BTs and STTs: high risk of post-resection hematoma leading to colonization with microbiota anaerobic bacteria [9], radiotherapy prior to surgery causing tissue hypo-oxygenation [10] and resection of tumors located near the pelvis that can lead to breaches in the digestive tract [11]. Few microbiological data on STTs are available in the literature. Only the study of Morii et al. [6] reported seven cases of STT patients, four of them presenting with postoperative infection due to *S. aureus* (50% MRSA), two with gram-negative bacteria ($n = 2$) and one with polymicrobial infection. In our study, gram-positive bacteria were predominant in both BT (88%) and STT infections (86%).

Second, we found that gram-negative bacteria, e.g., Enterobacteriaceae, were significantly more frequently isolated in STT patients than in BT patients (55% vs. 26%). Differences in patient characteristics such as surgical treatment, presence or absence of prostheses, and other potential risk factors such as age, sex comorbidities [12] and radiotherapy could explain differences in the distribution of microbial spectra between BTs and STTs (and between osteomyelitis and cellulitis).

Our microbiological data concerning BTs ($n = 42$) are congruent with previous studies. Gram-positive bacteria were isolated in 88% of the BT patients in our study, as compared to 63% in the study by Angelini et al. [13]. Furthermore, in our study 71% of infections in BTs were polymicrobial, as compared to 26% [1] to 38% [10] of BTs and 74% of sacral BTs [14] reported by others. In prosthesis-associated nontumoral bone infections, monomicrobial infections—with a majority of staphylococci [2]—predominate, whereas in postsurgical BT infections the microbiological spectrum is often polymicrobial (38%) with gram-positive and -negative bacteria [13]. Staphylococci were predominant in BTs (76% in our study, similar to 85% in other reports [1, 6, 8, 15]), with *S. aureus* in 38% and CNS in 82% in our study.

Therefore, our study strengthens the need for efficient anti-staphylococcal therapy—always covering CNS—as empirical antibiotic treatment for infections after surgery for BTs. Gram-negative bacteria grew in only 26% of BT patients in our study, mostly in pelvic tumors, chordomas and early acute infections occurring <1 month after oncologic surgery compared to 37% in the former literature [11].

The dichotomy in our microbiological findings was clearer when comparing BTs and STTs and type of tumor surgery rather than osteomyelitis and cellulitis, suggesting that tumor type (BT/STT) and treatment (prosthesis/non-prosthesis), rather than postoperative infection time (early, late), should drive the choice of antibiotic treatment. Antibiotic therapy duration ≥6 weeks was more frequently associated with successful clinical outcome in BTs (and osteomyelitis) than a shorter duration (<6 weeks) of antibiotic therapy (53% vs. 16%; $P = 0.02$); therefore, we recommend at least a 6-week duration of antibiotic treatment in BT patients.

Several limitations of the present study should be acknowledged. First, it is a single-center retrospective study of limited size based on clinical practice. Second, BT and STT groups differed by several characteristics (such as sex, age at time of infection and the use of oncologic preoperative radiotherapy), although we believe that these factors had little influence on the bacteriological findings. Third, the definition of infection used in the present study might have resulted in the collection of cases with a wide range of infectious conditions, resulting in a less homogeneous population. However, the current study included a relatively large number of patients, presenting the largest patient group of postoperatively infected STTs patients ($n = 30$) until now, with a complementary recovery of data from bacteriological, clinical and histological files.

CONCLUSIONS

Among patients presenting with infection following malignant tumor resection, the microbiological spectrum of causative agents is more often polymicrobial and frequently involves gram-negative bacteria for STTs, whereas staphylococci are predominantly associated with post-BT infections. Thus, empirical antibiotic treatment of STT postoperative surgical site infections should ensure a large coverage of both gram-positive and -negative bacteria. For infections following BT surgical resection, empirical antibiotic treatment should be focused on staphylococci, supplemented with a coverage of gram-negative bacteria in the case of early acute infection, non-prosthetic infections or pelvic BT localization.

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Conflict of interest. L. M. Vos, P. C. Morand, D. Biau, D. Archambeau, L. Eyrolle, J. Loubinoux, V. Perut, P. Leclerc, J.

E. Arends, P. Anract and D. Salmon have nothing to disclose.

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