INCIDENCE ON COST AND DURATION OF THERAPY OF POSSIBLE POSTOPERATIVE WOUND INFECTIONS FROM TRAUMA WITH PROSTHETIC DEVICES, PREVENTIVELY TREATED AND UNTREATED, USING ANTIBACTERIAL GELS AT P.O. SAN GIULIANO, ASL NAPLES 2 NORTH.

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ABSTRACT

Introduction:
Bacterial infections associated with implanted biomaterials represent the most significant complication in orthopedics, and they constitute the primary reason for the failure of primary hip and knee prostheses.
The prevention of infections associated with implanted biomaterials should simultaneously focus on at least two objectives: inhibition of biofilm formation and minimization of suppression of the local immune response.
Some of the technologies proposed for this purpose in clinical practice have already shown strong evidence of antibacterial effectiveness, safety, and resistance. The time is ripe for further development and experimentation of these technologies in a clinical context.
Material and Methods:
The study was conducted by observing wounds within 6 months following the treatments, and the purpose of the work was to evaluate the cost and benefit aspects in patients treated with defensive antibacterial gels during orthopedic prosthetic and/or synthesis surgeries at the P.O. San Giuliano ASL Napoli 2 Nord. The aim was to assess the effectiveness of the treatment applied to patients who underwent orthopedic prosthetic and/or synthesis surgeries. The wound conditions of treated patients and untreated patients were compared at 6 months after orthopedic surgery. Simultaneously, the costs incurred by the National Health Service (SSN) and the related benefits obtained for the treated patients and untreated patients were also analyzed. This observational and retrospective study was conducted over 6 months on a cohort of 60 patients from the orthopedic department and outpatient clinic of P.O. San Giuliano ASL Napoli 2, who underwent post-traumatic interventions. The cohort was divided into two groups: Group A (gA) included 30 operated patients whose wounds and/or devices used were treated with gels designed for decontamination, aiming to prevent infections; Group B (gB) consisted of 30 operated patients who were not treated with any such device. The study involved a 6-month observation of both groups, evaluating the possible onset of infections, their duration (until complete healing, including potential complications), and the average cost of the necessary treatment (monitoring the use of drugs, medical supplies, and devices).A value scale was established based on the average cost incurred and the average treatment duration for each of the 4 levels on the scale.
Results:
At the end of the study period, 30 patients from the cohort were observed in group gA, and 30 in group gB.
Within group gA, 2 patients experienced infections that positioned them in the first two levels of the scale, while in group gB, 8 patients required treatment for infections that placed them at different levels of the scale based on the treatment received and its associated cost. The economic impact is significant and variable, depending on the extent of usage indications (e.g., applying the device alone or as a carrier in combination with antibiotics in all subjects undergoing primary and revision arthroplasty surgeries, or fracture osteosynthesis, or only in a subset of them, e.g., patients selected at risk of infections, subjects undergoing prosthesis reimplantation, osteosynthesis of open traumatic fractures, etc.).
Conclusions:
The management of an infection that develops after orthopedic prosthetic and/or synthesis surgery leads the patient to seek and rely on long-term medical follow-up visits and specialized nursing assistance. The total costs for the care of the 10 infected patients show that the overall expenditure related to the 8 patients in group gB is much

higher than that of the total 2 patients in group gA, both because of the fivefold difference in terms of number, which demonstrates how treatment with antibacterial gel reduces the incidence of infections, and also because the infections that occurred in the case of the 2 patients in group gA are milder and more manageable.
Also considering the costs related to the use of antibacterial gel on wounds and/or prosthetic/osteosynthesis devices, the economic savings are still significant considering the cost of pharmacological treatments for infections and those for their potential complications.

INTRODUCTION

Bacterial infections related to implanted biomaterials represent the most significant complication in orthopedics and are the leading cause of failure in primary hip and knee prostheses.
The incidence varies between 0.5% and 4%, and it can occur even under excellent aseptic conditions with proper surgical procedures and adequate systemic antibiotic prophylaxis.
In traumatology, infectious complications after osteosynthesis occur in a percentage ranging from 0.5% to 25% of cases, depending on the type and site of fracture, the level of bone exposure, and the degree of soft tissue contusion.
The pathogenesis of infections from implanted devices or internal fixation devices is generally characterized by the bacterial capacity to colonize the surfaces of implant devices and various biomaterials, forming a biofilm. When the implant or surrounding tissue is contaminated, a "race to the surface" occurs between host cells and bacteria.
Compared to immune system cells, bacteria have the advantage of faster reproductive processes and extreme adaptability to the environment; bacterial colonization can form a protective biofilm within hours after initial adhesion to any implanted device.
Preventing infections associated with implanted biomaterials should simultaneously focus on at least two objectives: inhibiting biofilm formation and minimizing suppression of the local immune response.
A wide range of substances and technological approaches for antibacterial treatment of surfaces in orthopedic surgery have been proposed and tested for their antibacterial characteristics. A change in the chemistry and/or structure of the prosthetic surface can be achieved either chemically or physically by altering the surface layer of the existing biomaterial (e.g., through oxidation or

STRATEGY	FEATURES	EXAMPLES
Prevention in adhesion and adsorption		Anti-adhesive polymers
		Albumin
		Super-hydrophobic surface
		Hydrogels
Methods to kill bacteria	Inorganic	Silver nanoparticels
		Titanium dioxide
		Selenium Ion
		Copper ion
		Zinc ion
	Organic	Coated or covalently linked antibiotics
		Chitosan derivatives
		Cytokines
		Enzymes
	Other	Non-antibiotic bacterial substances
	Combined	Multilayer coating
		Sinergy material intensification
		Positively charged polymers
Multi-Functional and smart coating	Passive	Nanostructured “smart” material
	Active	Concept: sensors conjoined to nanoconainers
Alternative approach		Lytic bacteriophages

Table 1: *Types of Antibacterial Devices in Use (Source: Gallo J, Holinka M, Moucha CS. Antibacterial Surface Treatment for Orthopaedic Implants. Int. J. Mol.)*

mechanical modifications such as roughening/polishing/texturing). Another method involves overlaying the existing surface with a new thin layer of material having a different composition (e.g., hydroxyapatite coating, antibiotics covalently bonded to a substrate, attachment of other antimicrobial compounds).
In terms of durability, we can distinguish between degradable and non-degradable biomaterials.
Table 1 provides examples of proposed anti-infective strategies for antibacterial treatment of implantable surfaces used in orthopedic surgery (source: Gallo J, Holinka M, Moucha CS. Antibacterial Surface Treatment for Orthopaedic Implants. Int. J. Mol.).
In the literature, there are several studies focused on innovative strategies and techniques proposed for antibacterial treatment of implantable surfaces used in orthopedic surgery, presenting current knowledge on antimicrobial surface treatments aimed at preventing prosthetic infections. From these studies, it emerges that in the field of superficial antibacterial treatment of orthopedic implants, various potentially promising technologies have demonstrated efficacy both in vitro and in vivo:
• Some interfere with bacterial adhesion and the initial stages of biofilm formation;
• Others exhibit direct antibacterial properties.
The issues related to the mechanical properties of these technologies and potential adverse effects, such as toxicity and interference with osteointegration, require further investigation.
Some of the proposed technologies have already provided fairly strong evidence of antibacterial effectiveness, safety, and resilience. The time is ripe for further development and clinical experimentation of these technologies.
In selected studies evaluating individual substances composing the gel (hyaluronic acid and polylactic acid), the individual components in combination with antibiotics were tested in vitro.
In the in vitro study by Aviv (2007), polylactic acid, in hydrogel associated with gentamicin, released antibiotic concentrations over time effective against bacterial species known to be involved in orthopedic infections.
In the in vitro study by HU (2010), titanium surfaces (Ti) were functionalized with carboxymethyl chitosan (CMCS) or hyaluronic acid-catechol (HAC);
Vascular endothelial growth factor (VEGF) was then conjugated to the surfaces of grafted polysaccharides.
The antibacterial test with Staphylococcus aureus (S. aureus) showed that polysaccharide-modified substrates with VEGF significantly reduced bacterial adhesion.
Recently, a rapidly absorbable and biocompatible hyaluronic acid-derived biopolymer hydrogel has been patented.
The multinational project "A Novel Approach to Implant-Related Infections in Orthopedics and Trauma Surgery" has developed and validated a resorbable and antibacterial coating to prevent implant-related infections during orthopedic and trauma surgery. The hydrogel was designed to allow antibiotics to be loaded intraoperatively. This prevents bacterial colonization and biofilm formation, minimizing the risk of emerging drug-resistant bacterial strains.
The project members evaluated the safety, costs, efficacy, ease of use, durability, and sterilization of the hydrogel. Two clinical trials focusing on hip and knee arthroplasty and trauma surgery were successfully completed during the final phase of the project. Researchers confirmed the quality, durability, and safety of the products and validated sterilization using beta irradiation.
In vitro tests were conducted to assess the effectiveness of products preloaded with antibacterial agents. Tested antibacterial agents include compounds such as vancomycin, gentamicin, tobramycin, amikacin, and N-acetylcysteine (NAC). Good antibiofilm activity was observed against pathogens like Staphylococcus aureus and Staphylococcus epidermidis, without any cytotoxicity.
The project prototypes demonstrated promising results in terms of graft adhesion, particularly in human trials using deceased subjects' femurs or in vivo studies on rabbits. In addition to biocompatibility, successful procedures for product preparation and application were designed and tested.
Clinical studies (randomized, single-blind, controlled, multicenter, international) related to traumatology and arthroplasty, along with 12-month follow-up monitoring, have been concluded. The results showed a statistically significant difference between the group treated with antibacterial gel products and the control group.
Effectiveness: No infections were reported in the group treated with I.D.A.C. products, while 7.5% of the control group developed an infection ($p = 0.0023$). Regarding safety, no adverse events related to the product were observed.

MATERIALS AND METODS

The study was conducted by observing wounds over the 6 months following treatments (Follow-Up). The aim of the study was to assess the cost and benefit aspects in patients treated with defensive antibacterial gels during orthopedic procedures involving prostheses and/or synthesis at P.O. San Giuliano ASL Napoli 2 Nord. The primary objective was to evaluate the effectiveness of the treatment.
The states of the wounds were compared at 6 months post-orthopedic intervention between patients treated with antibacterial gels and those not treated. Simultaneously, the costs incurred by the National Health Service (NHS) and the corresponding benefits obtained from the treated patients and the untreated patients were evaluated.

The observational and retrospective study was conducted over 6 months on a cohort of 60 patients from the orthopedic department and clinic at P.O. San Giuliano ASL Napoli 2, who underwent post-traumatic interventions. The cohort was divided into 2 groups:

All patients in the individual groups were numbered with Roman numerals in ascending order, starting with those from gA and followed by those from gB.

GROUP	OPERATED	TREATTED	N°PATIENTS	OSTEOSYNTHESIS	PROSTHESES
gA	YES	YES	30	21	9
gB	YES	NO	30	23	7

Tab 2: *Division into groups of operated patients comprising the study cohort based on whether they received antibacterial gel treatment or not.*

In Group A (gA), 30 operated patients were included, whose wounds and/or devices used were treated with gel aimed at decontamination to prevent infections. In Group B (gB), 30 operated patients were included who were not treated with any device for this purpose.
The study involved observing the two groups for six months and evaluating the occurrence of infections, their duration (until complete healing, including any complications), and the average cost of the necessary treatment (monitoring the use of drugs, medical supplies, and devices). A scale of values was then set up.

LEVEL	AVERAGE COST	AVERAGE TREATMENT DURATION
L1	< 400 €	< 30 giorni
L2	401<€>1000	60<giorni>120
L3	1001<€ >2000	>90 giorni
L4	> 2000 €	≥ 120 giorni

Tab 3 - *Scale of values for the occurrence of potential infections observed during the 6-month Follow Up with average variables of duration and average therapy cost*

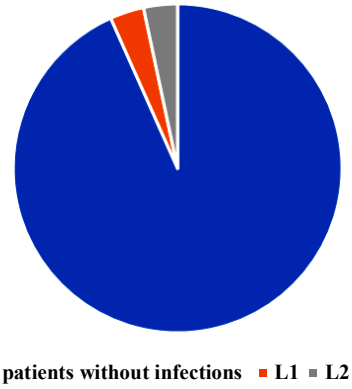
1. At Level 1 (L1), all patients in the cohort whose average therapy cost was less than €400 and with an average treatment duration of less than one month were placed.
2. At Level 2 (L2), all those for whom the therapy cost was between €401 and €1000 and the treatment duration was between 2 and 4 months were placed.
3. At Level 3 (L3), those with a therapy cost between €1001 and €2000 and a recovery time of 3 months were placed.
4. At Level 4 (L4), the remaining patients with a therapy cost >€2000 and a treatment duration ≥4 months were placed.

RESULTS

At the end of the 6-month observation period, it was possible to verify that:

- In gA, out of the 30 patients included, 1 patient experienced infections that placed them at Level 1 of the scale, and 1 other patient was placed at Level 2;

Distribution of the 30 patients in group gA with respect to the value scale.



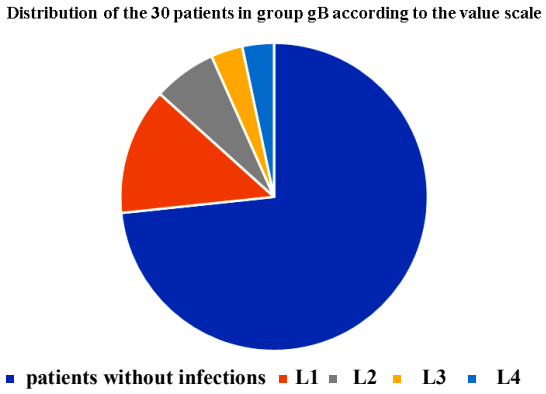
Graph 1: *Distribution of gA patients according to the value scale.*

The patient placed in L1, around 28 years old, who underwent osteosynthesis surgery, had to undergo a treatment with intramuscular cefalosporin for about 10 days using cefazolin. They changed dressings daily with wound healing and antiseptic activities, disinfecting with iodopovidone and water.
The one placed in L2, who underwent arthroplasty surgery, was administered vancomycin for 7 days in the hospital and intramuscular cefalosporin for 12 days at home. Due to a complication arising from treating early-stage pressure sores with silver ion spray, attributed to their not very young age (75 years), they also used dressings to promote healing at intervals of about 24 to 36 hours, disinfecting with iodopovidone and water.

gA	Patient N°	AVERAGE COST MEDIAN	TREATMENT DURATION	OSTEOSYNTHESIS	PROSTHETIC
L1	N° I	129 €	14 days	YES	
L2	N° II	535 €	67 days		YES

Table 4: *Specifics of Group gA*

Out of the 30 patients in group gB, 8 patients required treatment for occurred infections, and within this context, their placement on the value scale is as follows: 4 patients in L1, 1 patient in L2, 1 patient in L3, and 1 patient in L4.



Graph 2: *Distribution of gB patients in relation to the value scale*

Among the patients who underwent surgery but were not treated with antibacterial gel, the treatment costs are higher, the occurrence of infection is more frequent, and their severity is generally more significant and demanding. Patient III, a 19-year-old who underwent osteosynthesis, was placed in L1 due to the onset of a mild infection treated with intramuscular cephalosporins and wound care with disinfection. Patients IV and V, who underwent prosthetic interventions, experienced slightly more significant infections, requiring initial intravenous vancomycin treatment and post-discharge intramuscular cephalosporin administration. Patient VI had a slower recovery due to complications, influenced by his Type II diabetes. Two patients, VII and VIII, were placed in L2; one underwent osteosynthesis and the other prosthetic surgery. Patient VIII was initially treated with linezolid and later with vancomycin, followed by intramuscular cephalosporins and advanced wound care at home. Specifically, for Patient VIII, wound vacuum-assisted closure treatments were administered every two weeks. In the last two cases, Patients IX and X, hospitalization and treatment with meropenem became necessary after linezolid and vancomycin did not yield the desired outcomes. These patients also underwent treatment for pressure ulcers using silver-soaked dressings and sprays, followed by intramuscular antibiotic therapy at home. Additionally, they received continuous irrigation with specific solutions, negative pressure wound therapy, and even advanced wound care until complete healing..
The economic impact is high and variable depending on the treatment and its duration, the potential hospitalization of the patient, and its duration.

gB	Patient N°	AVERAGE COST MEDIAN	TREATMENT DURATION	OSTHEOSYNTESIS	PROSTHETICS
L1	N° III	230 €	18 days	YES	
L1	N° IV	398 €	22 days		YES
L1	N° V	412 €	25 days		YES
L1	N° VI	524 €	28 days	YES	
L2	N° VII	857 €	73 days	YES	
L2	N° VIII	924 €	86 days		YES
L3	N° IX	2350 €	94 days	YES	
L4	N° X	3783 €	131 days	YES	

Tab 5: *Specifics of gB*

CONCLUSIONS

The management of an infection that develops after orthopedic joint replacement and/or fixation surgery leads the patient to seek and rely on long-term medical check-ups and specialized nursing care.

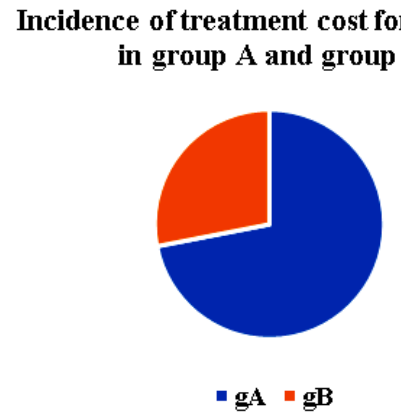
For the management of infected wounds resulting from orthopedic interventions, the National Health Service (SSN) incurs an average expense of around 800 million euros.

If a hip operation costs an average of 9 thousand euros, in the case of severe infections, the final cost can be much higher, for example:

Type of Hip Prosthesis Surgery	Cost in Eu-
15 days of acute hospitalization	9100,00 €
5 consultations for the wound	451.85 €
3 hematological consultations	271.11 €
7 infectious disease consultations	632.59 €
Clinical laboratory monitoring	134,13 €
Antibiotic therapy	3936,66 €
Total Costs	**14.526,34** €

Tab. 5: *Treatment cost about an infection after an Hip Prothesis Surgery (livello 3)*

The total costs for the treatment of the 10 infected patients highlight that the overall expenditure for the 8 from group gB (7051 euros) is significantly higher compared to the total of the 2 from group gA (664 euros), both due to being five times larger in terms of number, which demonstrates how treatment with antibacterial gels reduces the occurrence of infections, but also because the infections that occurred in the case of the 2 patients in group gA are much milder and more manageable.



Graf. 3 : *Treatment Cost in each group considering the total*

Also considering the costs related to the use of antibacterial gel (approximately 590 euros per kit) on wounds and/or prosthetic/osteosynthesis devices, the economic savings are still significant, given the cost of pharmacological treatments for infections and those for their potential complications.

Group	Treatment Cost	T.C.+Gel Antibatterico
gA	664 €	(590€x2) +664 €=1884 €
gB	7051 €	7051 €
Totals	**-6387 €**	**-5167 €**

Table 6: *Cost of Pharmacological Treatment + Cost of Disinfectant Gel Device*

Despite some recommendations having been identified for the better management of cutaneous wounds, there is currently no specific therapy for treating such lesions. Well-designed clinical studies with sufficiently large sample sizes are quite rare, and most treatments are used routinely even without reliable evidence of their effectiveness. As of now, the Italian National Institute of Health (Istituto Superiore di Sanità) has not published anything in this regard, partly because international guidelines need to undergo a specific process of adaptation before being incorporated into our clinical practice.

On average, specialized centers with high patient influx and large implant volumes provide:

- Environmental cleanliness
- Speedy interventions
- Use of antimicrobial gels before wound closure
- Management of post-operative dressings by experienced personnel

This patient-centered care tends to be more comprehensive in high-volume centers compared to those with smaller patient volumes. In the international literature, it is observed that low-volume prosthetic centers in peripheral areas, or those with relatively low prosthetic surgery numbers, tend to develop more complications, including infections, when compared to high-volume prosthetic surgery hospitals.

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