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FULL PAPER

Environmental factors associated with etiology of microbiologically confirmed reconstructive breast implant infections: impact on clinical management and treatment

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SUMMARY

Even if wide differences exist in the incidence of Gram-negative infections following breast cancer implant reconstructions (2-20%), its occurrence needs to be considered to optimize antibiotic therapy, which is usually directed towards Gram-positive cocci. There is a general notion on the possible source of Gram-negative microorganisms during outdoor activities. For this reason, we administered a specific questionnaire to infected patients to investigate this aspect.

In 450 consecutive implant reconstructions between January 1, 2016 and March 31, 2018, 27 patients (6%) developed proven infection. For each patient, we collected age, tumor stage and recurrence, chemo/radiotherapy, infecting microorganism, fate of implant, type and duration of antibiotic treatment, and administered a questionnaire on exposure to contaminated environments.

Twenty patients (74%) had Gram-positive and 7 (26%) had implants infected by Gram-negative agents. The two groups were homogeneous as regards age and no statistically significant difference was observed for other parameters. A significant difference was detected with regard to environmental risk factors in the Gram-negative group (p=0,049). Length of antibiotic therapy was longer in the Gram-negative patients (17.4 vs 11.05 days) and antibiotic treatment was ineffective in 43% of the Gram-negative group.

Environmental factors may be an element to evaluate in order to improve patient management. Surveys on larger cohorts are warranted.

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INTRODUCTION

Infection of implants after breast reconstruction in cancer patients is reported to occur with wide variability depending on the study design, with incidences ranging from 4.5% in retrospective surveys to 35% in some unstructured studies (Chidester, 2016; Phillips, 2016). Recent reports on prospective studies report a more reliable risk of infection of 6-10% after this procedure (Azouz, 2018; Franchelli, 2018). Diffusion of infection generally occurs by contiguity from the skin or from breast tissues in early infections (Cohen, 2015; Washer, 2012), while hematogenous dissemination from distant foci is more common in late infections (Chang, 2011).

Implant infection is commonly caused by Gram-positive pathogens, such as Staphylococcus aureus or coagulase-negative staphylococci (Washer, 2012). Staphylococci represent up to 80% of identified microorganisms in breast implant infections. These findings are consistent with other data from skin and soft tissue and joint prosthetic infections (Murphy, 2013; Trampuz, 2005; Zetrenne, 2007). The possible although minor occurrence of Gram-negative infections represents a negligible proportion of breast implant infections (2-20%) while a higher proportion of Gram-negative agents (up to 30%) has been occasionally reported (Seng, 2015; Franchelli, 2012; Weichman, 2013), thus suggesting that its possible occurrence be considered at the time of diagnosis. The need to also account for Gram-negative microorganisms at the time of initial empiric treatment is highlighted by the observation that these lead more frequently to implant loss with failure of reconstruction (Spear, 2010; Franchelli, 2015).

Factors that have been associated in recent years with increased risk of infection after breast reconstruction in cancer patients include BMI, tobacco use, diabetes, axillary dissection, chemo- and radio-therapy (Olsen, 2008; McCarthy, 2008). So far, however, there has been no acknowledgement of parameters associated with an increased risk of breast implant infection by Gram-negative microorganisms that could help in the clinical management of these patients. Conditions and environmental exposures that may lead to colonization by otherwise unusual pathogens contaminating implants

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Table 1 - *Comparison of clinical parameters observed in patients with microbiologically confirmed breast implant infections after reconstructive surgery in cancer patients.*

	Gram Positive Isolates	*Gram Negative Isolates*	*p- value*
N (%)	20 (74%)	7 (26%)	
Medium age	59	60	
Chemotherapy [N (%)]	4 (20)	2 (28,5)	0,633
Radiotherapy [N (%)]	5 (25)	1 (14,3)	1
Stage 0-1 [N (%)]	6 (30)	3 (43)	0,65
Stage 2-4 [N (%)]	8 (40)	2 (28)	0,67
Enviromental [N (%)]	3 (15)	4 (57)	0,049
Implant failure [N (%)]	7 (35)	4 (57)	0,391
Days of antibiotic therapy (Mean±SD)	11 + 0,92	17 + 1,08	0,0121
Average implant survival, days [M(±SEM)]	521,26 (89,8)	218,71 (86,4)	0,12852
Ineffective initial antibiotic therapy	3 (15)	3 (43)	0,28

have been reported and include specific Gram-negative microorganisms or Mycobacteria derived from contaminated series (Cicilioni, 2013; Scheflan, 2016; Jitmuang, 2017). For example, swimming-pools, whirlpool baths, aquariums, and spas have been described as a source of different microbial species that may cause a variety of respiratory, cutaneous/dermal, or central nervous system infections (Nichols, 2006; Papadopoulou, 2008; Smith, 2012). Gram-negative microorganisms may dwell preferentially in soil, plants, flowers, and aquariums, and can be encountered more frequently by patients who have outdoor activities and hobbies that include contact with soil, plants and fish.

In order to study whether specific risk factors may be detected in patients with breast reconstruction and implant infections by Gram-negative agents, and whether this risk may be identified, all patients with confirmed implant infection within a cohort of prospectively recruited patients at our Institute were administered a questionnaire investigating their potential exposure to environments in which Gram-negative pathogens are commonly present, and clinical course was compared for all patients stratified by infecting agent Gram stain.

PATIENTS AND METHODS

Between January 1, 2016 and March 31, 2018, 450 consecutive patients underwent immediate or delayed breast reconstruction using implants after mastectomy or expander replacement at our Institute. Clinical data of all patients are kept on record and were used for the analysis.

All implants had textured surfaces and were provided by Mentor and Allergan. Antibiotic prophylaxis using Cefalotin 14/20 mg/kg (1 gr followed by 2 doses q8h) was administered. For patients allergic to beta-lactams, Clindamycin was used. Implant infection was defined as previously described (Franchelli, 2012). For the present analysis, we considered only patients with proven infections (27/450 pts; 6%). The following data were considered for each patient: age, tumor stage and recurrence, chemo/radiotherapy, infecting microorganism, fate of implant, type and duration of antibiotic treatment. All causative microorganisms were identified using routine microbiologic methods and susceptibility tests were interpreted according to EUCAST breakpoints. Moreover, all patients with proven infection were also asked to answer a questionnaire with the aim of discovering some types of activities/hobbies that might expose them to particular types of microorganisms, such as rural residence, activities related to farming, livestock or fishing, recreational use of aquarium or spa. Statistical analysis was performed using two-sided tests: Chi-square analysis or Fisher's exact test and Mann-Whitney U-test were used to test the differences between groups.

RESULTS

Out of 27 patients (median age 59.5), 20 (74%) had a proven Gram-positive infection, while Gram-negative microorganisms were isolated in 7 cases (26%). Five patients had polymicrobial implant infection. The two groups were homogeneous with regard to age. When polymicrobial infections occurred and Gram-negative microorganisms were isolated, the episode was assigned to the Gram-negative group. Implant loss with removal occurred in four patients with Gram-negative infection and in seven patients with Gram-positive infection (57% vs 35%, p=0.391). Length of antibiotic treatment in the two groups (Mean±SEM) averaged 17±1.08 days in the Gram-negative group and 11±0.92 days in those with Gram-positive isolates (P=0.0121, Mann-Whitney U-test) (*Table 1*). Gram-negative infections were sustained by E. coli (1 pt), Leuconostoc mesenteroides (1pt), Acinetobacter spp (1pt), Sphyngomonas (1pt), Moraxiella osleolensis (1pt), P. mirabilis (1pt), and E cloacae (1pt). None of these bacteria had multiple drug resistance patterns. Although no P. aeruginosa was detected according to this list, these could be a link to community Gram-negatives as shown by the presence of Acinetobacter, Sphingomonas, Leuconostoc, and P. mirabilis.

When we investigated whether differences could be detected in commonly evaluated risk factors leading to infection, including age, chemo/radiotherapy, and tumor stage, no association with Gram-negative microorganisms was observed. With regard to fate of implant, a longer but not significant survival was observed for breast implants after salvage treatment for Gram-positive bacteria compared to those after treatment for Gram-negative bacteria (521±89 vs 218±86 days, Mean±SEM, P=0.152).

When environmental risk factors according to the ques-

Table 2 - *Reported activities potentially associated with environmental exposure to Gram negative bacteria in the patients with microbiologically confirmed breast implant infection after immediate reconstruction, stratified by Gram stain of the infecting agent.*

	Gram positive isolates (20)	*Gram negative isolates (7)*
Activities		
I am a farmer	1	1
I usually do gardening		1 (+ 2)
I tend courtyard animals/ livestock?		
I am a butcher/ fish-monger	1	1
I usually go fishing		
I have an aquarium		
I live in a countryside	1	1
I usually go to swimming pool/spas		
Total	3/20	4/7

tionnaire were considered, a significant difference was detected for environmental factors among patients with confirmed prosthetic device infections due to Gram-negative microorganisms (p= 0.049) (*Table 2*).

DISCUSSION

In the present work we observed an association between Gram-negative implant infections and possible environmental exposure in patients undergoing reconstructive surgery for breast cancer. In addition, a longer duration of treatment was recorded for breast implant infections undergoing salvage treatment following Gram-negative infections. Although Gram-negative bacteria represent in some series about 25% of germs isolated (Seng, 2015; Franchelli, 2012; Weichman, 2013; Spear, 2010; Franchelli, 2015), they are generally considered to represent a minority of causative bacteria. Indeed, breast implant infections are determined in the vast majority of cases by early infections (<2 months from surgery) due to Gram-positive bacteria (Washer, 2012), with *S.aureus* as the most frequently isolated pathogen and *S.epidermidis* as a possible alternative (Oliveira, 2018). These findings justify current empiric antibiotic prophylaxis protocols targeting this pathogen(s) without the need for Gram-negative coverage. In our series, patients with infections sustained by Gram-negative bacteria underwent longer duration of antibiotic treatment compared to those with Gram-positive infections (17 vs 11 days). This fact could be associated with the need to adjust initial empiric therapy targeting Gram-positive infections following receipt of culture results and suggests that Gram-negative breast implant infections may delay effective antibiotic treatment.

Another aspect to be considered in choosing antibiotic therapy is that Gram-negative infection may associate more frequently to implant loss. In the present series, the limited cohort size does not warrant this conclusion even if larger proportions of failures to preserve the implant pocket were observed (57% vs 35%, Gram-negative *vs* Gram-positive; not statistically significant). Interestingly, in this regard, the present finding of longer duration of antibiotic treatment coupled with decreased average implant survival is in line with the higher severity of infection in this group even if we could not document higher invasiveness of Gram-negative infections.

Larger multi-cohort studies are needed to clarify this issue. So far, when evaluating cancer patients for breast reconstruction, estimates of risk of implant encompass acknowledged parameters including age, weight, diabetes, hypertension, tumor stage, chemotherapy, radiotherapy. The present work suggests that an increased risk to develop Gram-negative infection may be associated with predisposing environmental risk factors. Ad hoc interviews that include the risk factors associated with possible colonization by Gram-negative bacteria may therefore help to better identify breast cancer patients at increased risk of implant infection by Gram-negative germs.

The present work suffers from some limitations that need to be mentioned for a correct perspective. Although the number of procedures was high (450), only 27 episodes of proven implant infections could be included in this analysis. This small number is a good indicator for procedural appropriateness; however, a larger patient size is needed to provide a more accurate estimate of the presently described association. In addition, later cohorts are needed to verify and validate the more adverse clinical course of patients with infection of breast implants by Gram-negatives that were here found to lead to apparently longer antibiotic treatment and higher proportions of implant loss. Another limitation is represented by the retrospective analysis. Although we keep a complete record of all procedures to avoid selection bias, a prospective evaluation on a higher number of infections would further clarify the risk of environmental exposure for Gram-negative infections, including the vast majority of patients who do not experience implant infection.

Based on the present observation, we conclude that the identification of environmental factors associated with Gram-negative colonization/implant infection is possible and represents a promising element to be included in the routine anamnestic questionnaire to patients. This observation however has a limitation, since the present finding is supported by a questionnaire, while there is no evidence of Gram-negative colonization at a pre-surgical screening. So far, there are no recommendations for pre-surgical cutaneous swab screening in cancer patients undergoing breast reconstruction, since this may be inefficient and costly due to the high number needed to find positive swabs if applied to the general population. Including a Gram-negative exposure questionnaire could improve patient management, particularly if "at risk" patients could be confirmed by screening for Gram-negative carriage at the time of hospital admission. Finally, if these findings could be confirmed in larger multi-center prospective studies, one could envision the use of antibiotics with anti-Gram-negative spectrum during empiric antibiotic treatment in patients who had risk factors pursuant to the questionnaire. Adapting this factor in clinical practice may contribute to shorter hospital stay and increased implant pocket retention.

Conflicts of interest

The authors declare no conflict of interest.

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