BMJ Open

Prophylactic treatment of breast implants with a solution of gentamicin, vancomycin and cefazolin antibiotics for women undergoing breast reconstructive surgery: protocol for a randomised, double-blind, placebo-controlled trial (The BREAST-AB trial)

Mathilde Nejrup Hemmingsen ,[1] Andreas Larsen,[1] Tim K Weltz,[1] Mathias Ørholt,[1] Sebastian Wiberg,[2] Anne Karen Bennedsen,[1] Camilla Bille,[3] Lena Felicia Carstensen,[4] Lisa Toft Jensen,[1] Rikke Bredgaard,[5] Vibeke Koudahl,[6] Volker Jürgen Schmidt,[7,8] Peter Vester-Glowinski,[1] Lisbet Rosenkrantz Hölmich,[5,8] Søren J Sørensen ,[9] Thomas Bjarnsholt,[10,11] Tine Damsgaard,[1,8] Mikkel Herly[1,10]

To cite: Hemmingsen MN, Larsen A, Weltz TK, *et al*. Prophylactic treatment of breast implants with a solution of gentamicin, vancomycin and cefazolin antibiotics for women undergoing breast reconstructive surgery: protocol for a randomised, double-blind, placebo-controlled trial (The BREAST-AB trial). *BMJ Open* 2022;**12**:e058697. doi:10.1136/bmjopen-2021-058697

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058697).

Received 27 October 2021
Accepted 30 August 2022

For numbered affiliations see end of article.

Correspondence to
Dr Mathilde Nejrup Hemmingsen; mathilde.nejrup.hemmingsen@regionh.dk

ABSTRACT

Introduction Periprosthetic infection is one of the most severe complications following implant-based breast reconstruction affecting 5%–10% of the women. Currently, many surgeons apply antibiotics locally on the breast implant to reduce the risk of postoperative infection, but no randomised, placebo-controlled trials have tested the treatment's efficacy.

Methods and analysis The BREAST-AB trial (BREAST-AntiBiotics) is an investigator-initiated, multicentre, randomised, placebo-controlled, double-blind trial of local treatment with gentamicin, vancomycin and cefazolin on breast implants in women undergoing implant-based breast reconstruction. The trial drug consists of 80 mg gentamicin, 1 g vancomycin and 1 g cefazolin dissolved in 500 mL of isotonic saline. The placebo solution consists of 500 mL isotonic saline. The trial drug is used to wash the dissected tissue pocket and the breast implant prior to insertion. The primary outcome is all-cause explantation of the breast implant within 180 days after the breast reconstruction surgery. This excludes cases where the implant is replaced with a new permanent implant, for example, for cosmetic reasons. Key long-term outcomes include capsular contracture and quality of life. The trial started on 26 January 2021 and is currently recruiting.

Ethics and dissemination The trial was approved by the Regional Ethics Committee of the Capital Region (H-20056592) on 1 January 2021 and the Danish Medicines Agency (2020070016) on 2 August 2020. The main paper will include the primary and secondary outcomes and will be submitted to an international peer-reviewed journal.

Trial registration number NCT04731025.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will include all types of patients undergoing breast reconstruction surgery with implants which makes the results relevant for all women undergoing implant-based breast reconstruction.
⇒ The randomised design will ensure an even distribution of risk factors in the placebo and intervention group, which will isolate the intervention's effect on the outcome.
⇒ The women undergoing bilateral breast reconstruction will receive antibiotic treatment to one of their breasts and placebo to the contralateral breast which isolates the effect of the trial drug from inter-individual variation.
⇒ The trial is evaluated with endpoints that are of great importance for patients.
⇒ The incidence of the primary outcome is relatively low, so despite the large sample size, a small effect of the treatment may not be detected with statistical significance.

INTRODUCTION

Breast reconstruction has been shown to improve a woman's quality of life after undergoing breast cancer surgery.[1] An increasing number of women choose implant-based breast reconstruction,[2] which includes a risk of implant infection. Implant infection is seen in 5%–10% of the women,[3–7] and the treatment typically requires removal of the implant

after which the patient must wait several months before a new breast reconstruction can be attempted.

Previous studies suggest that bacterial contamination of the breast implant can occur without any clinical symptoms.[8 9] Instead, the bacteria form a chronic, subclinical infection which is suspected to cause a prolonged immune reaction to the implant called capsular contracture, which affects up to 10%–20% of the patients.[10 11] Capsular contracture causes hardening and deformity of the breast, and the treatment often includes surgical removal of the contracted capsule and exchange of the implant.

Surgeons have attempted numerous strategies to prevent bacterial contamination of the implant.[12–17] The most widely followed approach is to apply antibiotics directly on the breast implant and in the dissected tissue pocket during the surgery,[18] but only few studies have investigated the clinical effect of the treatment. A recent meta-analysis found a decreased rate of implant infection and capsular contracture in women treated with antibiotics applied on the breast implant.[19] However, the included studies were mostly retrospective and varied greatly in the applied antibiotics, control groups and follow-up period. Furthermore, no randomised controlled trials were identified in the meta-analysis.[19]

Due to the limited evidence, The Centers for Disease Control and Prevention (CDC) guideline for the prevention of surgical site infection has no recommendations regarding the use of locally applied antibiotics on implants[20] and The National Institute for Health and Care Excellence in England has requested further studies investigating the clinical effect of the treatment.[21] Randomised clinical trials are essential for developing evidence-based treatment guidelines. The BREAST-AB trial is designed to assess the effect of locally applied antibiotics on all-cause loss of the implant after implant-based breast reconstruction. We hypothesise that local application of gentamicin, vancomycin and cefazolin decrease the risk of postoperative clinical infections and thereby reduce the risk of losing the implant to the benefit of women undergoing implant-based breast reconstruction.

METHODS AND ANALYSIS

The protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement[22] and the International Conference on Harmonisation Good Clinical Practice guidelines.[23] The protocol is provided in full length in online supplemental file 1.

Trial design

The BREAST-AB trial is an investigator-initiated, multicentre, randomised, double-blind, placebo-controlled trial investigating local application of gentamicin, vancomycin and cefazolin during implant-based breast reconstruction. The antibiotic solution or placebo is applied directly onto the breast implant and in the dissected tissue pocket during the surgery.

Setting

The trial will be conducted at six hospitals in Denmark, and additional trial sites may be included during the trial period (see online supplemental file 1 for a list of the trial sites).

Eligibility criteria

The trial will include all types of patients undergoing breast reconstruction surgery with implants which makes the results relevant for all women undergoing implant-based breast reconstruction. Patients that meet the following criteria are considered eligible for inclusion:

- Age ≥18.
- Biologically female.
- Written informed consent.
- Scheduled for breast reconstruction with implants or expanders including
  - Immediate or delayed reconstruction.
  - Unilateral or bilateral reconstruction.
  - With or without simultaneous flap reconstruction.

Exclusion criteria are:

- Pregnancy.
- Breast feeding.
- Known allergy towards gentamicin, vancomycin, cefazolin or neomycin.
- Known anaphylactic reaction towards beta-lactam antibiotics or aminoglycosides.
- Myasthenia gravis.
- Known impaired renal function, GFR (Glomerular Filtration Rate) <60 mL/min.
- Participation in investigational drug trials concerning disinfection agents in the breast cavity.

Trial intervention

The trial drug contains 80 mg gentamicin, 1000 mg vancomycin and 1000 mg cefazolin dissolved in an infusion bag containing 500 mL of sterile isotonic saline. The placebo solution consists of 500 mL sterile isotonic saline contained in a similar infusion bag. Both solutions are achromatic, and the infusion bags are indistinguishable from one another. See figure 1 for an illustration of the trial intervention.

During the surgery, the responsible nurse draws 150 mL from the assigned infusion bag and the plastic surgeon uses it to wash the dissected tissue pocket.[24] Another 50 mL are drawn from the same infusion bag and used to soak the implant prior to insertion in the tissue pocket. The rest of the content in the infusion bag is discarded.

Randomisation

The trial drug and placebo are assigned in a 1:1 ratio. Patients undergoing unilateral breast reconstruction are randomised to either the trial drug or placebo, whereas patients who undergo bilateral breast reconstruction are randomised to the trial drug on one breast and placebo on the contralateral breast. The paired design involving

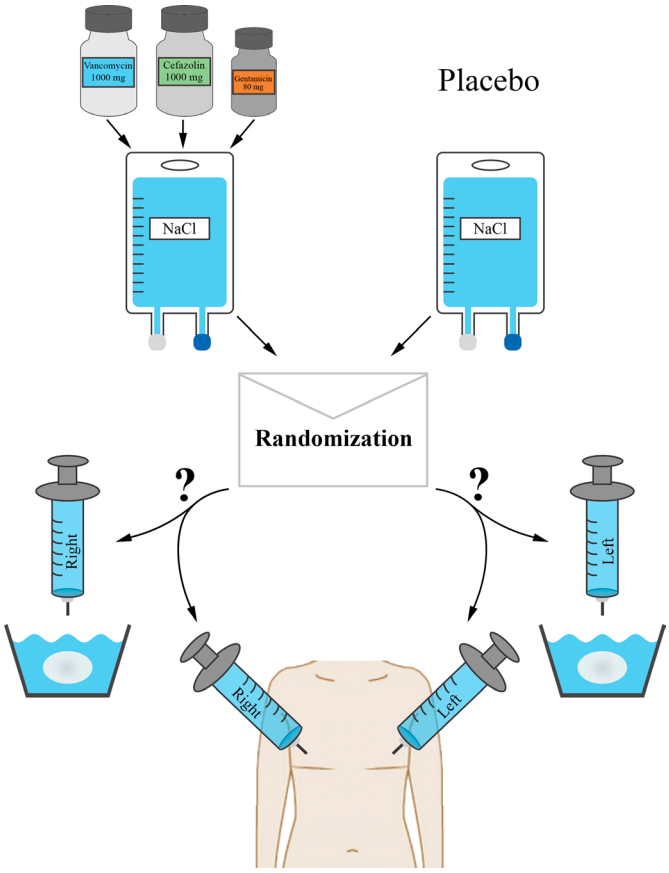

Figure 1 Illustration of the trial intervention. The trial drug contains 1000 mg vancomycin, 1000 mg cefazolin and 80 mg gentamicin dissolved in an infusion bag containing 500 mL of sterile isotonic saline. The placebo solution consists of 500 mL sterile isotonic saline.

the patients undergoing bilateral surgery isolates the effect of the trial treatment from the interindividual variation, as these patients serve as their own control. Patients who undergo two-stage breast reconstruction with an expander implant, which is replaced with a permanent implant after 3–6 months, are allocated to the same trial treatment during both surgeries (see figure 2 for an overview of the trial design).

The randomisation is stratified according to study site, whether the patients undergo unilateral or bilateral surgery, and selected risk factors based on the literature[25] including radiation therapy and immediate vs delayed reconstruction. This approach ensures an even distribution of the selected risk factors in the placebo group and the intervention group. The randomised design will ensure that other potential risk factors, which are not included in the stratification, are evenly distributed in the intervention and control group. The treatment is assigned in a fixed block size of two to ensure that the trial drug and placebo are evenly distributed within each stratum.

Blinding

The trial is double-blind so that the patients, site investigators, healthcare personnel and the data assessors are blinded to the allocated treatment. The only unblind investigators are the nurses responsible for preparing the trial drugs and the members of the trial coordination unit who provide the treatment allocation. The designated nurse prepares the trial drugs before the surgery. The trial drugs are prepared outside of the operating room to make sure that the surgeon and the surgical staff are blinded to the treatment. The unblind investigators do not take part in any treatment-related procedures, clinical evaluation of the outcomes or data assessment. In case of emergency unblinding, the trial coordination unit will provide the allocation assignment under discretion of the treating physician.

Primary outcome

All-cause explantation of the breast implant within 180 days after the breast reconstruction

All-cause explantation is defined as explantation and discarding of the breast implant. However, the following cases are not counted as explantation: replacement of an expander with a permanent implant; and replacement of a permanent breast implant with a new permanent breast implant due to cosmetic revisions such as asymmetry, implant malposition, change of size or implant rotation.

The rationale for the primary outcome is to quantify whether the locally applied antibiotics prevent severe infection or other complications that leads to loss of

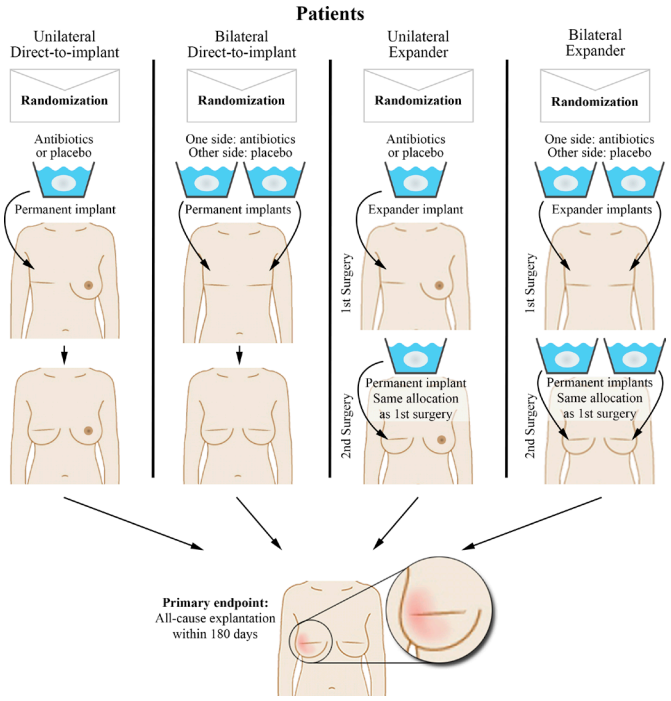

Figure 2 Overview of the trial design. The patients are randomised to antibiotic treatment or placebo applied directly onto the breast implant and in the dissected tissue pocket. Patients who undergo bilateral breast reconstruction are randomised to antibiotics on one side and placebo on the contralateral side. Patients who undergo unilateral breast reconstruction are randomised to either antibiotics or placebo.

the reconstruction within 180 days after surgery. Sometimes, the indication for explantation of the implant may be ambiguous because multiple complications can occur simultaneously. Therefore, all-cause explantation was chosen as a more objective alternative to infection that leads to explantation of the implant. The primary outcome does not include explantation and direct placement of a new permanent implant for cosmetic reasons because revisional surgery is not considered a proxy for severe complications that may be affected by antibiotics on the implant.

The definition of explantation for cosmetic reasons and discarding of the breast implant was revised in the protocol V.2.8, dated 10 May 2022, from only mentioning asymmetry and implant rotation to include all types of implant malposition and change of implant size.

Secondary outcomes

Time to explantation

Time to explantation is defined as the number of days from the reconstructive surgery to the surgical removal of the implant. This outcome was chosen because local application of antibiotics may delay the development of a postoperative clinical infection.

All-cause explantation of the breast implant within 1 year after the breast reconstruction surgery (Y/N)

Previous studies[26] suggest that surgical removal of the permanent implant can occur up to 1 year after the surgery, and therefore, this is included as a secondary outcome.

Revision surgery with incision of the fibrous capsule after the breast reconstruction surgery

This is defined as all revisional surgery that includes exposure of the breast implant. This outcome was included because the breast reconstruction in some cases can be upheld with revisional surgery despite complications that may be associated with low-virulent bacteria.

Exchange of the permanent implant with an expander implant after the breast reconstructive surgery

This subgroup consists of patients who undergo a salvage procedure, where the permanent implant is removed and discarded, and the implant pocket is cleansed and irrigated with antiseptic agents (eg, a solution of hydrogen peroxide) after which an expander implant is inserted to prevent the tissue envelope from contracting while still preserving the vulnerable skin flaps. This group will be counted in the primary outcome, but we hypothesise that the patients chosen for this treatment option may have less severe symptoms of infection and may have concomitant necrosis due to poor blood supply to the skin flaps. Therefore, the effect of the treatment in this subgroup may be modest compared with the patients who have explantation without replacing it with an expander.

Surgical site infection that leads to antibiotic treatment within 180 days after the breast reconstruction

Surgical site infection is defined according to the CDC classification.[27] The clinical signs of infection are combined with the prescription of antibiotics as a confirmation of the surgeons suspicion of infection. Additional outcome measures are listed in online supplemental file 1 and on ClinicalTrials.gov.

Long-term outcomes

The trial includes a long-term assessment of capsular contracture after 5, 10 and 15 years. The use of locally applied antibiotics could potentially decrease the rate of capsular contracture by minimising or altering the low-virulent bacterial contamination of the implant. Therefore, capsular contracture is an important long-term outcome.

The trial also evaluates long-term quality of life using the BREAST-Q questionnaire 'Reconstruction Module'.[28] The preoperative questionnaire is administered after the patient has provided informed consent. The postoperative questionnaire is administered 3 months, 1 year and 5 years postoperatively. The application of local antibiotics may decrease the risk of postoperative complications and thereby decrease the risk of undergoing revision surgery. This in turn may lead to improved patient satisfaction and quality of life. BREAST-Q is a validated tool used to quantify patient satisfaction and health-related quality of life after breast reconstruction surgery.

Sample size

The trial is powered to find a 5% risk reduction in the primary outcome. Based on the literature, the assumed rate of implant loss in the control group is 10%.[6 7] The independent sample unit is 'breast', because previous data do not suggest that implant loss is correlated between the two breasts of a patient.[3] Therefore, the power of the trial is based on the number of breasts, so that the final number of included patients depends on the proportion of patients who undergo bilateral breast reconstruction. With an alpha of 0.05, the trial will have a power of 0.90 to detect an absolute risk reduction of 5% with 1158 breasts. To account for drop-out of up to 10%, we will include patients with a combined estimated number of 1274 breasts in the trial. We expect 27% of the patients to undergo bilateral breast reconstruction (based on unpublished data) and, therefore, 1003 patients will be included in the trial.

Statistical analysis plan

The statistical analyses and reporting will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[29] All statistical analyses will be conducted on a modified intention-to-treat population defined as all patients that have been allocated to the study drug and have a valid informed consent.

The primary outcome and key secondary outcomes are categorical variables and will be presented as frequencies

in each group. The overall effect of the intervention on the primary and secondary outcomes will be modelled as both univariate and multivariate mixed effects logistic regression models considering the correlation between breasts in patients undergoing bilateral surgery. The results will be presented as crude and adjusted ORs with 95% CIs. The model will be adjusted for potential confounders, including age, smoking, body mass index, trial site and indication for surgery (prophylactic mastectomy vs mastectomy after cancer diagnosis). The full statistical analysis plan is provided in the protocol in online supplemental file 1.

Data collection and follow-up

All patients are admitted to the hospital for approximately 3 days after the surgery. All patients are scheduled for postoperative follow-up visits after approximately 3 months and 1 year. Data on drug administration are obtained real time and entered in an electronic case report form. Additional data are obtained from the patients' medical records by trained researchers and entered in the electronic case report form. A list of included variables is provided in the protocol in online supplemental file 1.

Clinical treatment

Participation in the trial will not interfere with any clinical decisions regarding the treatment of the patients, and all other clinical treatment than the trial treatment, including preoperatively, perioperatively and postoperatively administered medicine, will adhere to the standard treatment at each trial site. The randomised design and the stratified randomisation will ensure that potential risk factors which may influence the outcome are equally distributed in the placebo and intervention group.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Ethical considerations

The trial protocol has been reviewed and approved by the Regional Ethics Committee of the Capital Region (H-20056592) on 1 January 2021 and the Danish Medicines Agency (EudraCT 2020-002459-40) on 2 August 2020. The trial is monitored by the Good Clinical Practice units in Denmark.

There are currently no clinical guidelines in Denmark regarding the use of locally applied antibiotics on breast implants, and the treatment depends on the individual surgeon's preference. Allocation to placebo in this trial is therefore considered ethically acceptable. A detailed description of the ethical considerations is provided in online supplemental file 1.

Safety considerations

Previous studies have shown that the serum level after local application of antibiotics is low,[30 31] and therefore, the risk of systemic side effects is low. Gentamicin, vancomycin and cefazolin have been used for local application on breast implants for many years and are considered safe.[16 32] If the patients experience adverse events, it will be registered in an electronic case report form in REDCap and treated according to local guidelines. All serious adverse reactions will be reported yearly to the Danish Medicines Agency and the Regional Ethics Committee by the sponsor-investigator during the study period. A more detailed description of the safety considerations is provided in the protocol in online supplemental file 1.

Consent

Consent from trial participants is obtained according to Danish legislation.[33] The investigators are responsible for obtaining the signed, informed consent from the patients prior to any protocol-related activities. The consent can be withdrawn by the patient at any time and without explanation, after which the patient will receive the standard treatment according to the local guidelines. An example of the patient consent form is provided in online supplemental files 2 and 3.

Dissemination

The main paper will include the primary and secondary outcomes. The manuscript will adhere to the CONSORT guidelines and will be used to report the results of the trial to the scientific community. The manuscript will be submitted to an international peer-reviewed journal, and both positive, negative and inconclusive results will be published. The findings of the trial will be shared with participating sites and presented at national and international conferences. The results will be registered at ClinicalTrials.gov and will be disseminated to the public.

Status

The first patient was enrolled in the trial in January 2021, and the trial is currently recruiting. The last patient is expected to be included in January 2025. The primary results of the trial are anticipated in July 2025 after the last patient's last follow-up. The results from this trial can be used in evidence-based treatment guidelines for implant-based breast reconstruction surgery.

Author affiliations

[1]Department of Plastic Surgery and Burns Treatment, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[2]Department of Anaesthesiology, Zealand University Hospital Koge, Køge, Denmark
[3]Department of Plastic Reconstructive Surgery, Odense University Hospital, Odense, Denmark
[4]Department of Plastic Surgery, Southwest Jutland Hospital, Esbjerg, Denmark
[5]Department of Plastic Surgery and Burns Treatment, Herlev og Gentofte, Copenhagen University Hospital, Herlev, Denmark
[6]Department of Plastic Surgery, Lillebaelt Hospital, Vejle, Denmark
[7]Department of Plastic and Breast Surgery, Zealand University Hospital Roskilde, Roskilde, Denmark
[8]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[9]Department of Biology, Section of Microbiology, University of Copenhagen, Copenhagen, Denmark
[10]Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark

[11]Department of Clinical Microbiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contributors All authors took part in designing the trial and writing the trial protocol. MNH, AL, TKW and AKB constitute the trial coordinating unit who are responsible for coordinating all trial related activities. MNH wrote the manuscript. MH is the coordinating principal investigator of the trial and the local site investigator at Rigshospitalet. He has critically revised and contributed to the final version of the manuscript. TD, SJS, TB, PVV-G and MH are members of the trial steering committee and they have all revised and approved the final manuscript. CB, RB, LFC, LRH, LTJ, VK and VJS are local site investigators and they have revised and approved the final manuscript. MØ and SW are members of the blinded data assessment committee and have provided statistical expertise to the trial design and contributed with writing the statistics sections and have revised and approved the final manuscript.

Funding MH is the initiator and sponsor of the trial. The trial is supported by the Novo Nordisk Foundation (grant number 0058322, grant holder Tine Damsgaard) and the Medicine Fund of the Danish Regions (grant number R-189-A4127, grant holder MH).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Mathilde Nejrup Hemmingsen http://orcid.org/0000-0002-8439-6537
Søren J Sørensen http://orcid.org/0000-0001-6227-9906

REFERENCES

1 Eltahir Y, Werners LLCH, Dreise MM, *et al*. Quality-Of-Life outcomes between mastectomy alone and breast reconstruction: comparison of patient-reported BREAST-Q and other health-related quality-of-life measures. *Plast Reconstr Surg* 2013;132:201e–9.
2 American Society of Plastic Surgeons. 2019 plastic surgery statistics report, 2019. Available: https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-full-report-2019.pdf
3 Coroneos CJ, Selber JC, Offodile AC, *et al*. US FDA breast implant postapproval studies: long-term outcomes in 99,993 patients. *Ann Surg* 2019;269:30–6.
4 Stevens WG, Calobrace MB, Alizadeh K, *et al*. Ten-Year core study data for Sientra's food and drug Administration-approved round and shaped breast implants with cohesive silicone gel. *Plast Reconstr Surg* 2018;141:7S–19.
5 Maxwell GP, Van Natta BW, Bengtson BP, *et al*. Ten-Year results from the Natrelle 410 anatomical Form-Stable silicone breast implant core study. *Aesthet Surg J* 2015;35:145–55.
6 Petersen A, Eftekhari ALB, Damsgaard TE. Immediate breast reconstruction: a retrospective study with emphasis on complications and risk factors. *J Plast Surg Hand Surg* 2012;46:344–8.
7 Dikmans REG, Negenborn VL, Bouman M-B, *et al*. Two-Stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol* 2017;18:251–8.
8 Pajkos A, Deva AK, Vickery K, *et al*. Detection of subclinical infection in significant breast implant capsules. *Plast Reconstr Surg* 2003;111:1605–11.
9 Rieger UM, Mesina J, Kalbermatten DF, *et al*. Bacterial biofilms and capsular contracture in patients with breast implants. *Br J Surg* 2013;100:768–74.
10 Benediktsson K, Perbeck L. Capsular contracture around saline-filled and textured subcutaneously-placed implants in irradiated and non-irradiated breast cancer patients: five years of monitoring of a prospective trial. *J Plast Reconstr Aesthet Surg* 2006;59:27–34.
11 Calobrace MB, Stevens WG, Capizzi PJ, *et al*. Risk factor analysis for capsular contracture: a 10-year sientra study using round, smooth, and textured implants for breast augmentation. *Plast Reconstr Surg* 2018;141:pp. 20S–28.
12 Chopra K, Gowda AU, McNichols CHL, *et al*. Antimicrobial prophylaxis practice patterns in breast augmentation: a national survey of current practice. *Ann Plast Surg* 2017;78:629–32.
13 Yalanis GC, Liu E-W, Cheng H-T. Efficacy and safety of povidone-iodine irrigation in reducing the risk of capsular contracture in aesthetic breast augmentation: a systematic review and meta-analysis. *Plast Reconstr Surg* 2015;136:687–98.
14 Kenna DM, Irojah BB, Mudge K, *et al*. Absorbable antibiotic beads prophylaxis in immediate breast reconstruction. *Plast Reconstr Surg* 2018;141:486e–92.
15 Nava MB, Catanuto G, Rocco N. Reply: role of mitomycin C in preventing capsular contracture in implant-based reconstructive breast surgery: a randomized controlled trial. *Plast Reconstr Surg* 2017;140:823e–4.
16 Hunsicker LM, Chavez-Abraham V, Berry C, *et al*. Efficacy of Vancomycin-based continuous triple antibiotic irrigation in immediate, implant-based breast reconstruction. *Plast Reconstr Surg Glob Open* 2017;5:e1624.
17 Tutela JP, Duncan DP, Kelishadi SS, *et al*. Continuous postoperative antibiotic irrigation via catheter system following immediate breast reconstruction. *Eplasty* 2015;15, :e49.
18 Hidalgo DA, Sinno S. Current trends and controversies in breast augmentation. *Plast Reconstr Surg* 2016;137:1142–50.
19 Lynch JM, Sebai ME, Rodriguez-Unda NA, *et al*. Breast pocket irrigation with antibiotic solution at implant insertion: a systematic review and meta-analysis. *Aesthetic Plast Surg* 2018;42:1179–86.
20 Berríos-Torres SI, Umscheid CA, Bratzler DW, *et al*. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg* 2017;152:784–91.
21 National Institute for Health and Care Excellence (NICE). Surgical site infections: prevention and treatment. Available: https://www.nice.org.uk/guidance/ng125/chapter/Recommendations#intraoperative-phase
22 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
23 . I. C. H. H. T. guideline, general considerations for clinical trials E8. *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 1997.
24 Adams WP, Rios JL, Smith SJ. Enhancing patient outcomes in aesthetic and reconstructive breast surgery using triple antibiotic breast irrigation: six-year prospective clinical study. *Plast Reconstr Surg* 2006;117:46S–52.
25 Olsen MA, Nickel KB, Fox IK, *et al*. Comparison of wound complications after immediate, delayed, and secondary breast reconstruction procedures. *JAMA Surg* 2017;152, :e172338.
26 Kalstrup J, Balslev Willert C, Brinch-Møller Weitemeyer M, *et al*. Immediate direct-to-implant breast reconstruction with acellular dermal matrix: evaluation of complications and safety. *Breast* 2021;60:192–8.
27 TC H, "Gaynes H, Martone WJ, Jarvis WR, *et al*. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections,". *Infect Control Hosp Epidemiol* 1992;13:pp. 606–608.
28 Pusic AL, Klassen AF, Scott AM, *et al*. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg* 2009;124:345–53.
29 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials* 2010;11:32.
30 Sweet FA, Roh M, Sliva C. Intrawound application of vancomycin for prophylaxis in instrumented thoracolumbar fusions: efficacy, drug levels, and patient outcomes. *Spine* 2011;36:2084–8.
31 White RR, Pitzer KD, Fader RC, *et al*. Pharmacokinetics of topical and intravenous cefazolin in patients with clean surgical wounds. *Plast Reconstr Surg* 2008;122:1773–9.

32 Campbell CA. The role of Triple-Antibiotic saline irrigation in breast implant surgery. *Ann Plast Surg* 2018;80:S398–402.
33 Retsinformation. Lov om et videnskabsetisk komitesystem og behandling af biomedicinske forskningsprojekter, 2003. Available: https://www.retsinformation.dk/eli/lta/2003/402 [Accessed 19 Apr 2021].