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Use of Prophylactic Closed Incision Negative Pressure Therapy Is Associated with Reduced Surgical Site Infections in Gynecologic Oncology Patients Undergoing Laparotomy

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Condensation: In this retrospective case-control study, closed incision negative pressure dressings following laparotomy for gynecologic cancer are associated with decreased surgical site infection versus standard dressings

Short Title: Use of prophylactic closed incision negative pressure dressings following laparotomy in gynecologic oncology

AJOG At A Glance:

A: The objective was to determine whether prophylactic closed incision negative pressure therapy (ciNPT) dressings are associated with a decreased risk of surgical site infection in gynecologic oncology patients undergoing laparotomy compared to standard surgical site dressings.

B: In this retrospective, case-control study, use of ciNPT was associated with a significant reduction in superficial incisional and deep incisional surgical site infections compared to standard dressings.

C. Use of ciNPT may be considered for surgical site infection risk-reduction in high-risk patients undergoing laparotomy for known or suspected gynecologic cancers.

Abstract

Background: Surgical site infection following surgery for gynecologic cancer increases morbidity. Prophylactic closed incision negative pressure therapy (ciNPT) has shown promise in decreasing infectious wound complications across many surgical disciplines.

Objective(s): To determine whether ciNPT is associated with reduced surgical site infection in gynecologic oncology patients undergoing laparotomy compared to standard dressings.

Study Design: This was a retrospective case-control study in patients undergoing laparotomy for known or suspected gynecologic cancer from 1/1/2017-2/1/2020. Patients were matched in a 1:3 ratio (ciNPT: standard dressing) by body mass index, age, diabetes, bowel surgery, smoking and steroid use. Surgical site infection was defined according to the Centers for Disease Control. Multivariable logistic regression using backward selection was performed.

Results: Of 1223 eligible laparotomies, 64 (5.2%) received ciNPT dressings and were matched to 192 (15.7%) controls. There were no differences in medical co-morbidities ($p>0.05$), site or stage of malignancy ($p>0.05$), length of surgery ($p=0.82$) or surgical procedures ($p>0.05$). Use of ciNPT was associated with reduction in all adverse wound outcomes (20.3% vs. 40.1%, $p<0.001$). Specifically, ciNPT was associated with a significant reduction in both superficial incisional surgical site infections (9.4% vs. 29.7%, $p<0.001$) and deep incisional surgical site infections (0.0% vs. 6.8%, $p=0.04$). On multivariable analysis, ciNPT use was associated with significant reduction in the

incidence in superficial incisional infections alone (OR 0.29, 0.12-0.73, p=0.008) and both superficial or deep incisional infections (OR 0.29, 0.12-0.71, p=0.007).

Conclusion(s): In this retrospective case-control study, use of prophylactic ciNPT following laparotomy in gynecologic oncology patients is associated with decreased superficial incisional and deep incisional infections compared to standard dressings. Furthremore, ciNPT was associated with reduction in all other wound adverse outcomes. ciNPT may be considered for surgical site infection prevention in high-risk gynecologic oncology patients undergoing laparotomy.

Keywords: gynecologic oncology, surgical site infection, closed incision negative pressure therapy, laparotomy

Introduction

Surgical site infections (SSIs) are a leading cause of health-care associated morbidity, accounting for up to 40% of nosocomial infections [1]. In gynecologic cancer patients undergoing laparotomy, SSI rates as high as 30% have been reported [2]. SSI following surgery for gynecologic cancer is associated with longer hospital stay, readmission, re-operation and increased healthcare costs [3-7]. Over the last decade, investigators have sought to identify modifiable risk factors and interventions in efforts to reduce infection rates. Women who are obese, malnourished or who have bowel surgery appear to be at highest risk for SSI [3-9]. Several promising strategies including suture closure and antimicrobial skin glue have failed to improve outcomes [10,11]. SSI remains a significant problem despite implementation of infection reduction bundles, protocols to improve post-operative glycemic control and use of immuno-nutrition, [12-20].

Prophylactic closed incision negative pressure therapy (ciNPT) dressings have shown promise in decreasing infectious wound complications across many other surgical disciplines [21-27]. A randomized, controlled, open-label study by O'Leary et al. in patients undergoing laparotomy for general surgery, colorectal or gynecology procedures found that the incidence of SSI was significantly decreased from 32.0% to. 8.3% in patients who received ciNPT compared to controls [21]. Similarly, in a retrospective matched case control study of patients undergoing high-risk open colorectal surgery, prophylactic use of ciNPT significantly decreased the incidence of surgical site infection from 15% to 7% [24]. Likewise, a retrospective study by Zaidi et al. demonstrated a significant decrease in post-operative wound complications from

20.5% in those receiving conventional dressings to 2.9% in patient's receiving ciNPT [27].

To date, no studies have addressed whether ciNPT impacts infectious morbidity in gynecologic oncology patients. The purpose of the current study was to determine whether prophylactic ciNPT decreases the incidence of SSI in patients with known or suspected gynecologic cancer undergoing laparotomy, compared to standard dressings.

Materials and Methods

Study Design and Patient Matching

This was an IRB approved retrospective case-control study conducted at The Cleveland Clinic. Beginning in January 2017, customizable ciNPT dressings (Prevena Incision Management System, KCI, San Antonio, Texas, USA) were available for use at four sites within a multi-center hospital system. Decision to use prophylactic ciNPT dressing was at the discretion of the primary surgeon. There was no pre-defined criteria or randomization strategy employed to determine patients who received prophylactic ciNPT at the time of surgery. All included patients had vertical midline incisions; no mini-laparotomy incisions for tissue extraction were included in this study.

All patients who underwent laparotomy for known or suspected gynecologic cancer from January 1st 2017 – February 1st 2020 were identified. Demographics, surgical, and oncologic data were abstracted. All patients who received a ciNPT dressing, at the discretion of the surgeon, were included in the study. Patients were matched to controls who underwent laparotomy within the same time period. Control

patients were matched to those who had ciNPT dressings in a 3:1 ratio based upon decade of age (<30, 31-40, 41-50, 51-60, 61-70, >70 years), diabetes, body mass index (BMI) strata (<30, 31-40, 41-50, >50kg/m^2), small bowel and/or large bowel surgery, current smoking and current steroid use.

Surgical Procedure

All patients received the same pre-operative and post-operative care, including pre-operative antibiotic prophylaxis, with appropriate re-dosing. Chlorhexidine alcohol-based scrub and betadine was used for abdominal and vaginal preparation, respectively. The standard surgical closure was at the discretion of the operating surgeon. Fascial closure was performed with either a polydioxanone (PDS) suture in a looped running fashion or interrupted figure of eight or Polyethylene terephthalate suture utilizing interrupted figure of eights. Subcutaneous space was closed if >2 cm deep, followed by staple or suture closure of the skin. The ciNPT dressing was applied over the closed incision in the operating room under sterile conditions with suction pressure set to -125mmHg. The ciNPT dressings maintain negative pressure for seven days, and then automatically shut off and can be removed. ciNPT dressings are not routinely removed to inspect the incision, unless clinically indicated In patients who were discharged prior to 7 days the ciNPT dressing was kept in place and patients were provided with removal instructions on home going. ciNPT dressings were removed on post-operative day 7 in hospitalized patients. Standard dressings were applied following wound closure, and included either high viscosity tissue adhesive skin glue (Exofin, Chemence Medical) or adhesive bandage dressing (Primapore, Smith and Nephew) which are routinely removed on the second post-operative day.

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151

152 *Data Collection*

153 The EMR was reviewed for patient demographics, oncologic variables and
154 surgical characteristics, which included operative time, wound class, procedural details,
155 dose and timing of antibiotic prophylaxis, peri-operative transfusion and hyperglycemia.
156 Infectious wound outcomes were defined using Centers for Disease Control definitions:
157 superficial incisional SSI, deep incisional SSI and organ/space infections [1] (Table 1).
158 All patients were treated with antibiotics following surgical site infection diagnosis. The
159 primary outcome was assessment of adverse infectious wound outcomes which was
160 superficial incisional SSI within 30 days of surgery [1]. The secondary outcomes were
161 defined as: deep incisional SSI, organ/space infection, dehiscence, seroma and/or
162 hematoma, need for wound exploration or debridement, re-operation, readmission, ICU
163 admission, urinary tract infection, pneumonia, bacteremia, bowel or urinary leak within
164 30 days of surgery. All collected patient information was stored electronically using
165 REDCap (Research Electronic Data Capture) [28].

166 *Statistical Analysis*

167 A priori power calculation was performed to detect the primary outcome of
168 superficial incisional SSI with patients who received ciNPT dressings matched 1:3 to
169 controls to detect a difference as seen by O'Leary et al. (α=0.05 and β=0.80), P values
170 of < 0.05 were considered statistically significant. Approximately normally-distributed
171 continuous measures were summarized using means and standard deviations and
172 compared using two-sample t-tests. Continuous measures that show departure from

normality and ordinal measures were summarized using medians and compared using Wilcoxon rank sum tests. Categorical factors were summarized using frequencies and percentages and were compared using Pearson's chi-square tests or Fisher's Exact tests.

Two multivariable logistic regressions further explored the impacts of ciNPT dressings on the superficial incisional SSI, as well as the composite outcome of superficial incisional and deep incisional infections, controlling the factors which showed differences between two groups. Candidate variables including: age, body mass index (BMI) as a continuous variable, ASA score, medical comorbidities of hypertension, diabetes mellitus, hyperlipidemia and venous thromboembolism. Backward (p stay=0.05) and stepwise selection (p entry=0.15, p stay=0.05) yielded the same result for both models, ASA score and diabetes mellitus were kept in the final models. All analyses were completed using SAS (version 9.4, The SAS Institute, Cary, NC).

Results

From January 1, 2017 – February 1, 2020, 1223 laparotomies were performed in the gynecologic oncology division at The Cleveland Clinic. Of these patients, 64 (5.2%) had ciNPT dressings. Controls included 192 (15.7%) patients matched based on BMI, age, diabetes mellitus, steroid use, bowel surgery, and current smoking. Demographic characteristics for the ciNPT and standard dressing groups are shown in Table 2. There were no differences in race (p=0.10) or medical comorbdities (p>0.05). The proportion of patients with American Society of Anesthesiologists (ASA) score of 3 or 4 was statistically lower in the ciNPT patients compared to controls (57.8% vs. 78.6%,

p<0.001). There were no differences in pre-operative hemoglobin (p=0.73), hematocrit (p=0.47), albumin (p=0.48). In addition, there were no differences in hemoglobin A1c among those patients with diabetes mellitus (p=0.85).

The surgical and oncologic details for the ciNPT and control dressing groups are shown in Table 3. There were no significant differences in length of surgery (p=0.82), wound classification (p=0.74) or need for emergent surgery (p=0.37) between the two groups. In addition, there were no differences in surgical procedures including radical hysterectomy/en-bloc resection (p=0.34), small bowel (p=0.33) and large bowel surgery (p=079). Similarly, ileostomy (p=0.99) and colostomy (p=0.99) creation were similar between the groups. There were no significant differences in benign pathology (12.5% vs. 4.2%, p=0.06). In those with cancer, there was no difference between stage of disease (p=0.46) compared to controls. Receipt of neoadjuvant chemotherapy (27.5% vs. 28.0%, p=0.35) and post-operative radiation (10.9% vs 8.9%, p=0.45) were similar between for ciNPT compared to standard dressings

Post-operative outcomes including infectious complications are shown in Table 4. When compared to controls, the use of ciNPT dressings was associated with significant reduction in any adverse wound outcomes (20.3% vs. 40.1%, p<0.001). Specifically, ciNPT dressings were associated with a significantly lower rate of both superficial incisional (9.4% vs. 29.7%, p<0.001) and deep incisional SSI (0.0% vs. 6.8%, p=0.04). There was no significant difference in incidence of deep space or organ infection (0.0% vs. 4.7%, p=0.12) who received ciNPT dressings compared to controls. In addition, there was an non-significant decrease in overall incidence of skin dehiscence (7.8% vs. 16.7%, p=0.07) in patients who received ciNPT. Need for wound exploration was

significantly decreased in those who received ciNPT dressings compared to standard dressings (6.3% vs. 18.8%, p=0.02). There were no differences noted in other non-infectious adverse wound outcomes including seroma (4.7% vs. 6.8%, p=0.77) and hematoma (4.7% vs. 1.6%, p=0.15). In addition, there were no differences appreciated in non-wound related adverse post-operative outcomes, including re-operation (3.1% vs. 4.2%, p=0.99), readmission (17.2% vs. 17.7%, p=0.89) and ICU admission (15.6% vs. 15.6% %, p=0.96).

Table 5 displays results of univariate analysis for superficial incisional SSI. Use of ciNPT was associated with reduced incidence of superficial incisional SSI (9.4% vs. 29.7%; p<0.001). In addition, among the patients who developed superficial incisional SSI, higher incidence of ASA score of 3 or 4 (90.5% vs. 67.9%; p<0.001) and increased age (63.0 vs 59.6 years, p=0.04) were observed.

On multivariable analysis controlling for age, BMI, diabetes mellitus, bowel surgery and smoking, use of ciNPT dressings were associated with lower odds of post-operative superficial incisional SSI (OR 0.29, 95% 0.12-0.73, p=0.008). Similarly, the use of ciNPT dressings were associated with lower odds of the composite outcome including superficial incisional and deep incisional infections, (OR 0.29, 95% 0.12-0.71, p=0.007). In addition, ASA score of ¾ (OR 3.8, 95% CI 1.5-9.5, p=0.008) was associated with higher odds of superficial incisional SSI. Similar results considering the composite outcome of both superficial incisional and deep incisional SSI were seen for patients with ASA score 3/4 (OR 3.9, 95% CI 1.6-9.7, p=0.003)(Table 6).

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243

244 **Comments**

245 *Principal Findings*

246 In this retrospective case-control study, use of ciNPT was associated with a
247 significant reduction in superficial incisional and deep incisional SSI compared to
248 controls matched for age, BMI, smoking, bowel surgery and steroids. In addition, ASA
249 score of 3/4 was identified as predictors of higher risk of superficial incisional SSI or
250 deep incisional infections on multivariate analysis.

251 *Results*

252 In this retrospective case-control study of patients undergoing laparotomy for
253 suspected gynecologic cancer, the use of prophylactic ciNPT dressings was associated
254 with significantly lower incidence of all adverse wound events. Specifically, ciNPT
255 dressings were associated with significant reduction in both superficial incisional and
256 deep incisional SSI. On multivariate analysis, the reduced rate of SSI remained
257 significant. ciNPT use did not lead to differences in wound seromas or hematomas, nor
258 increases in the incidence of re-operation or readmission.

259 *Clinical Implications*

260 This is the first study to address the use of ciNPT in the gynecologic oncology
261 patient population. Our study demonstrated that ciNPT dressing were associated with
262 reduced incidence of superficial incisional SSI (OR 0.29, 95% 0.12-0.73, p=0.008).
263 Similarly, the use of ciNPT dressings were associated with lower odds of the composite
264 outcome including superficial incisional and deep incisional SSI (OR 0.29, 95% 0.12-

0.71, p=0.007). In the colorectal and general surgery literature, ciNPT have shown an improvement in SSI with prophylactic use. In a randomized controlled trial by O'Leary et al, patients undergoing laparotomy for general surgery, colorectal or gynecologic indications received either standard dressings (n=25) or ciNPT (n=25). In the trial, use of ciNPT was associated with significant reduction in SSI from 32.0% vs. 8.3% [21]. Similarly, in a retrospective case control study of patients undergoing laparotomy for colorectal disease who were matched for SSI risk factors, prophylactic use of ciNPT significantly decreased the incidence of surgical site incision from 15% to 7% [24]. Subsequently, Sahebally performed a meta-analysis, including three randomized trials, with 1266 unique patients who underwent laparotomy with primary closure by general and colorectal surgery [29]. In this meta-analysis, the use of ciNPT significantly improved SSI rates compared with standard dressings with OR of 0.25. Of nine included studies, eight strongly favored ciNPT for SSI risk reduction [29].

In recent years, many studies have been performed to optimize wound outcomes and reduce infections following laparotomy for gynecologic cancer. Of the studied interventions, infection prevention bundles (including skin preparation, pre-operative antibiotics and closing trays) have shown promising reductions in SSI incidence. In a prospective series of patients undergoing ovarian cancer debulking by Lippitt et al, use of the prevention bundle decreased SSI rates from 20% to 3% [15]. Similarly, in patients undergoing laparotomy with bowel surgery for gynecologic cancer, SSI rates were reduced from 37% to 12% following the bundled interventions. While effective, especially in patients with bowel surgery, bundled initiatives require a significant collaborative effort It also remains unclear which specific components of infection

bundles have most benefit for SSI reduction. In comparison, ciNPT dressings can be applied with ease in the operating room with minimal personnel and training and allowed for continued treatment after the patient is discharged. They may be considered as an adjunct to SSI reduction bundles in high-risk patients, including those with obesity, diabetes and ASA score 3 or 4. These factors have been reported as independent predictors of SSI in the current study and prior literature and are not modifiable in the operating room [3-9].

In addition to increased surgical morbidity, SSIs contribute to significant healthcare expenditures, with an estimated cost of 3.3 billion dollars annually [30]. In a study by Lewis et al., a decision tree was designed from a cohort of patients with endometrial cancer from 2002-2007 to assess whether prophylactic ciNPT would be cost-effective for SSI reduction [31]. The overall cost of incisional care was significantly lower among patients who received prophylactic ciNPT by $104 [31]. Within the overall cohort, they reported that incidence of wound complications must be reduced by 33% to be considered cost-effective [31]. In further analysis specifically for obese and morbidly obese patients, ciNPT resulted in increased savings and wound complication reduction per patient, with reduction rates of 28% and 25% required for cost-savings [31]. A similar study byChopra et al. performed a meta-analysis of 829 patients, 260 of whom received ciNPT compared to standard dressings for general surgery procedures [32]. They concluded that ciNPT may prove cost-effective when SSI rates exceed 16.4% [32]. In our study, ciNPT use far exceeded these cost-effectiveness thresholds identified by Lewis and Chopra et al., with a reduction in superficial incisional SSI from 29.7% to 9.4% (OR of 0.29) with ciNPT use. Given the high prevalence of SSI in

311 gynecologic cancer patients undergoing laparotomy, ciNPT use may prove cost-
312 effective in reducing healthcare costs associated with infectious morbidity, in addition to
313 the impact on short-term morbidity and long-term oncologic outcomes. It is important to
314 note that ciNPT dressings are easy to use, can be removed in any setting (clinic, home,
315 inpatient) and will automatically turn off after seven days, and therefore, do not require
316 additional home health care support.

317 *Strengths and Limitations*

318 There are several limitations to this study. First, this was a retrospective, non-
319 randomized study design with ciNPT application at the discretion of the primary
320 surgeon. Although ciNPT dressings were utilized by all surgeons within the gynecologic
321 oncology division during the study period, we are unable to draw conclusions regarding
322 whether rate of surgeon utilization impacted incisional outcomes. Nonetheless, the
323 possibility for selection bias cannot be excluded. In order to minimize the effect of
324 possible bias, we employed a rigorous matching strategy, which included age, BMI,
325 diabetes, bowel surgery, steroids and smoking to compare patients at similar SSI risk
326 based upon pre-defined risk factors for SSI [3-9]. We were unable to match for all risk
327 factors for SSI, including method of skin closure, pathology and ASA score given the
328 retrospective nature. While patients who received ciNPT dressings did not receive any
329 additional post-operative care compared to controls, we are unable to fully account for
330 this given the non-randomized study design. Our study was powered for the primary
331 outcome of superficial incisional SSI, and therefore, we are unable to draw conclusions
332 regarding whether ciNPT impacts other adverse wound outcomes, such as hematomas
333 and seromas. A further consideration is that the majority of the patients included in this

study were obese with ASA scores of 3 and 4, representing a group with higher baseline risk for infection. Therefore, these findings may be not generalizable to all patient undergoing laparotomy for gynecologic cancer. Nevertheless, this study is the first to report the impact of ciNPT following laparotomy for suspected gynecologic cancer and is hypothesis generating. We provide promising evidence that ciNPT dressings reduce risk of SSI, consistent with other surgical disciplines.

Research Implications

Prospective trials are in gynecologic oncology patients are ongoing, and will hopefully allow for further understanding of the utility of prophylactic ciNPT following laparotomy.

Conclusions

Within this large retrospective matched case-control study of women undergoing laparotomy for suspected gynecologic cancers, ciNPT dressings were independently associated with decreased risk of superficial incisional and deep incisional SSI compared to standard dressings. Patients with higher ASA scores seem to also be at an increased risk for infection, and may represent the population who may benefit most from ciNPT.

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References

1. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992 Oct;13(10):606-8.
2. Nugent, E.K., Hoff, J.T., Gao, F., Massad, L.S., Case, A., Zighelboim, I., Mutch, D.G., Thaker, P.H., Wound complications after gynecologic cancer surgery, Gynecol.Oncol. 121 (2011) 347-352
3. Mahdi H, Gojayev A, Buechel M, Knight J, SanMarco J, Lockhart D, et al. Surgical site infection in women undergoing surgery for gynecologic cancer. Int J Gynecol Cancer. 2014 May;24(4):779-86.
4. Tran, C.W., McGree, M.E., Weaver, A.L., Martin, J.R., Lemens, M.A., Cliby, W.A., Dowdy, S.C., Bakkum-Gamez, J.N., Surgical site infection after primary surgery for epithelial ovarian cancer: predictors and impact on survival, Gynecol.Oncol. 136 (2015) 278-284
5. Tuomi, T., Pasanen, A., Leminen, A., Butzow, R., Loukovaara, M., Incidence of and risk factors for surgical site infections in women undergoing hysterectomy for endometrial carcinoma, Acta Obstet.Gynecol.Scand. 95 (2016) 480-485

6. Uppal, S., Penn, C., Del Carmen, M.G., Rauh-Hain, J.A., Reynolds, R.K., Rice, L.W., Readmissions after major gynecologic oncology surgery, Gynecol.Oncol. 141 (2016) 287-292
7. Bakkum-Gamez, J.N., Dowdy, S.C., Borah, B.J., Haas, L.R., Mariani, A., Martin, J.R., Weaver, A.L., McGree, M.E., Cliby, W.A., Podratz, K.C., Predictors and costs of surgical site infections in patients with endometrial cancer, Gynecol.Oncol. 130 (2013) 100-106
8. Gunderson, C.C., Java, J., Moore, K.N., Walker, J.L., The impact of obesity on surgical staging, complications, and survival with uterine cancer: a Gynecologic Oncology Group LAP2 ancillary data study, Gynecol.Oncol. 133 (2014) 23-27
9. Bouwman, F., Smits, A., Lopes, A., Das, N., Pollard, A., Massuger, L., Bekkers, R., Galaal, K., The impact of BMI on surgical complications and outcomes in endometrial cancer surgery--an institutional study and systematic review of the literature, Gynecol.Oncol. 139 (2015) 369-376
10. Thomas, E.D., Nugent, E.K., MacAllister, M.C., Moxley, K.M., Landrum, L., L Walker, J., McMeekin, D.S., Mannel, R.S., McGwin, G., Moore, K.N., Effectiveness of cyanoacrylate microbial sealant in the reduction of surgical site infection in gynecologic oncology procedures: A phase III single institution prospective randomized trial, Gynecol.Oncol. 144 (2017) 193-199
11. Kuroki LM, Mullen MM, Massad LS, Wu N, Liu J, Mutch DG, et al. Wound Complication Rates After Staples or Suture for Midline Vertical Skin Closure in Obese Women: A Randomized Controlled Trial. Obstet Gynecol. 2017 Jul;130(1):91-9.

12. Al-Niaimi, A.N., Ahmed, M., Burish, N., Chackmakchy, S.A., Seo, S., Rose, S., Hartenbach, E., Kushner, D.M., Safdar, N., Rice, L., Connor, J., Intensive postoperative glucose control reduces the surgical site infection rates in gynecologic oncology patients, Gynecol.Oncol. 136 (2015) 71-76
13. Chapman, J.S., Roddy, E., Westhoff, G., Simons, E., Brooks, R., Ueda, S., Chen, L., Post-operative enteral immunonutrition for gynecologic oncology patients undergoing laparotomy decreases wound complications, Gynecol.Oncol. 137 (2015) 523-528
14. Hopkins, L., Brown-Broderick, J., Hearn, J., Malcolm, J., Chan, J., Hicks-Boucher, W., De Sousa, F., Walker, M.C., Gagne, S., Implementation of a referral to discharge glycemic control initiative for reduction of surgical site infections in gynecologic oncology patients, Gynecol.Oncol. 146 (2017) 228-233
15. Lippitt, M.H., Fairbairn, M.G., Matsuno, R., Stone, R.L., Tanner, E.J.,3rd, Wick, E.C., Angarita, A.C., Roche, K.L., Levinson, K.L., Bergstrom, J.E., Sinno, A.K., Curless, M.S., Wethington, S., Temkin, S.M., Efron, J., Hobson, D., Fader, A.N., Outcomes Associated With a Five-Point Surgical Site Infection Prevention Bundle in Women Undergoing Surgery for Ovarian Cancer, Obstet.Gynecol. 130 (2017) 756-764
16. Nguyen, J.M.V., Sadeghi, M., Gien, L.T., Covens, A., Kupets, R., Nathens, A.B., Vicus, D., Impact of a preventive bundle to reduce surgical site infections in gynecologic oncology, Gynecol.Oncol. 152 (2019) 480-485
17. Schiavone, M.B., Moukarzel, L., Leong, K., Zhou, Q.C., Afonso, A.M., Iasonos, A., Roche, K.L., Leitao, M.M.,Jr, Chi, D.S., Abu-Rustum, N.R., Zivanovic, O.,

Surgical site infection reduction bundle in patients with gynecologic cancer undergoing colon surgery, Gynecol.Oncol. 147 (2017) 115-119

18. Taylor, J.S., Marten, C.A., Munsell, M.F., Sun, C.C., Potts, K.A., Burzawa, J.K., Nick, A.M., Meyer, L.A., Myers, K., Bodurka, D.C., Aloia, T.A., Levenback, C.F., Lairson, D.R., Schmeler, K.M., The DISINFECT Initiative: Decreasing the Incidence of Surgical INFECTions in Gynecologic Oncology, Ann.Surg.Oncol. 24 (2017) 362-368
19. Kwaan MR, Weight CJ, Carda SJ, Mills-Hokanson A, Wood E, Rivard-Hunt C, et al. Abdominal closure protocol in colorectal, gynecologic oncology, and urology procedures: a randomized quality improvement trial. Am J Surg. 2016 Jun;211(6):1077-83.
20. Bruce SF, Carr DN, Burton ER, Sorosky JI, Shahin MS, Naglak MC, et al. Implementation of an abdominal closure bundle to reduce surgical site infection in patients on a gynecologic oncology service undergoing exploratory laparotomy. Gynecol Oncol. 2018 Jun;149(3):560-4.
21. O'Leary DP, Peirce C, Anglim B, Burton M, Concannon E, Carter M, et al. Prophylactic Negative Pressure Dressing Use in Closed Laparotomy Wounds Following Abdominal Operations: A Randomized, Controlled, Open-label Trial: The P.I.C.O. Trial. Ann Surg. 2017 Jun;265(6):1082-6.
22. Gupta R, Darby GC, Imagawa DK. Efficacy of Negative Pressure Wound Treatment in Preventing Surgical Site Infections after Whipple Procedures. Am Surg. 2017 Oct 1;83(10):1166-9.

23. Cooper HJ, Bas MA. Closed-Incision Negative-Pressure Therapy Versus Antimicrobial Dressings After Revision Hip and Knee Surgery: A Comparative Study. J Arthroplasty. 2016 May;31(5):1047-52.

24. Curran T, Alvarez D, Pastrana Del Valle J, Cataldo TE, Poylin V, Nagle D. Prophylactic closed-incision negative-pressure wound therapy is associated with decreased surgical site infection in high-risk colorectal surgery laparotomy wounds. Colorectal Dis. 2018 Jul 26.

25. Gombert A, Babilon M, Barbati ME, Keszei A, von Trotha KT, Jalaie H, et al. Closed Incision Negative Pressure Therapy Reduces Surgical Site Infections in Vascular Surgery: A Prospective Randomised Trial (AIMS Trial). Eur J Vasc Endovasc Surg. 2018 Jun 30.

26. Redfern RE, Cameron-Ruetz C, O'Drobinak SK, Chen JT, Beer KJ. Closed Incision Negative Pressure Therapy Effects on Postoperative Infection and Surgical Site Complication After Total Hip and Knee Arthroplasty. J Arthroplasty. 2017 Nov;32(11):3333-9.

27. Zaidi A, El-Masry S. Closed-incision negative-pressure therapy in high-risk general surgery patients following laparotomy: a retrospective study. Colorectal Dis. 2017 Mar;19(3):283-7.

28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377-81.

29. Sahebally SM, McKevitt K, Stephens I, Fitzpatrick F, Deasy J, Burke JP et al. Negative pressure wound therapy for closed laparotomy incisions in general and colorectal surgery: A systematic review and meta-analysis. JAMA Surg 2018; 153:e183467.
30. Surgical Site Infection Event. https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf.
31. Lewis LS, Convery PA, Bolac CS, Valea FA, Lowery WJ, Havrilesky LJ. Cost of care using prophylactic negative pressure wound vacuum on closed laparotomy incisions. Gynecol Oncol 2014; 132:684-9.
32. Chopra K, Gowda AU, Morrow C, Holton L,3rd, Singh DP. The economic impact of closed-incision negative-pressure therapy in high-risk abdominal incisions: A cost-utility analysis. Plast Reconstr Surg 2016; 137:1284-9.

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498 **Figure Legend**

499 **Table 1:** Centers for Disease Control Definitions for Surgical Site Infection

500 **Table 2:** Patient Demographics

501 **Table 3:** Oncologic and Surgical Details

502 **Table 4:** Infectious and Post-operative Outcomes

503 **Table 5**: Univariate Analysis for Post-Operative Superficial Incisional SSI

504 **Table 6**: Multivariable Analysis for Post-Operative Superficial Incisional SSI

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506 **Table 1**: Centers for Disease Control Definitions for Surgical Site Infection

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Infection Type	Definition
Superficial Incisional Surgical Site Infection	Infection of the skin and subcutaneous tissue of the incision with at least one of the following 1) purulent drainage, 2) positive wound culture or 3) incision that is deliberately opened by physician with pain, tenderness, swelling, erythema or heat within 30 days after surgery
Deep Incisional Surgical Site Infection	Infection that involves the deep tissues of the skin (fascia and muscle layers) with at least one of the following 1) purulent drainage, 2) deep incision that spontaneously dehisces or is deliberately opened by physician with positive wound culture and at least one of the following fever, pain or tenderness or 3) abscess or gross infection involving the deep incision that is detected on exam or imaging within 30 days of surgery
Deep/Organ Space Infection	Infection that involves any part of the body deeper than the fascia or muscle layers with 1) purulent drainage from drain placement into the organ or space, 2) positive culture or 3) abscess or other evidence of infection involving the organ/space detected on exam or imaging test suggestive of infection within 30 days after surgery

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509 Adapted from the Centers for Disease Control Definitions [1].

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531 **Table 2:** Patient Demographics
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Factor	All Patients (n=256)	ciNPT Dressing (n=64)	Standard Dressing (n=192)	P value
Age (years)	60.4 ± 11.8	59.0 ± 11.8	60.9 ± 11.8	0.27
Body Mass Index (kg/m2)				0.37
<30	65 (25.4)	14 (21.9)	51 (26.6)	
31-40	112 (43.8)	27 (42.2)	85 (44.3)	
41-50	71 (27.7)	19 (71.9)	52 (27.1)	
>51	8 (3.1)	4 (6.3)	4 (2.1)	
Race				0.10
White	212 (82.8)	52 (82.8)	160 (83.3)	
Black	36 (14.1)	8 (12.5)	28 (14.7)	
Asian	1 (0.4)	0 (0.0)	1 (0.5)	
Hispanic/Latino	2 (0.8)	0 (0.0)	2 (1.0)	
Indian/Middle Eastern	3 (1.2)	2 (3.1)	1 (0.5))	
Unknown	2 (0.8)	2 (3.1)	0 (0.0)	
ASA score				**<0.001**
1	8 (3.1)	7 (10.9)	1 (0.5)	
2	60 (23.4)	20 (31.3)	40 (20.8)	
3	177 (69.1)	36 (56.3)	141 (73.4)	
4	11 (4.3)	1 (1.6)	10 (5.2)	
Smoking				0.37
Current	20 (7.8)	4 (6.2)	16 (0.8)	
Historical	59 (23.0)	19 (29.2)	40 (20.9)	
None	177 (69.1)	42 (64.6)	135 (70.7)	
Medical Comorbidities				
HTN	136 (53.1)	40 (62.5)	96 (50.0)	0.11
DM	100 (39.1)	25 (39.0)	75 (39.1)	0.93
CKD	33 (12.9)	11 (17.2)	22 (11.5)	0.25
Pulmonary Disease	43 (16.8)	13 (20.3)	30 (15.6)	0.41
CAD	29 (11.3)	7 (10.9)	22 (11.5)	0.88
Prior MI	3 (1.2)	1 (1.6)	2 (1.0)	0.99
Prior Stroke	8 (3.1)	0 (0.0)	8 (4.2)	0.21
Prior VTE	36 (14.1)	11 (17.2)	25 (13.0)	0.25
Current TPN use	2 (0.8)	0 (0.0)	2 (1.0)	0.99
Current Steroid Use	5 (1.9)	2 (3.1)	3 (1.6)	0.60
Hemoglobin (g/dL)	11.7 [10.2, 13.1]	12.0 [10.0, 13.2]	11.7 [10.2, 13.0]	0.73

Hematocrit	36.4 [31.7, 40.0]	37.8 [31.9, 41.4]	36.1 [31.6, 39.6]	0.47
Albumin (g/dL)	4.0 [3.7, 4.3]	4.0 [3.6, 4.3]	4.0 [3.7, 4.3]	0.48
Creatinine (μmol/L)	0.79 [0.68, 0.94]	0.81 [0.70, 0.96]	0.79 [0.68, 0.91]	0.26
HbA1c (%) (n=26)	6.6 [5.9, 7.8]	6.7 [5.9, 8.2]	6.6 [6.1, 7.5]	0.96
Prior MRSA infection	8 (3.1)	4 (6.3)	4 (2.1)	0.21
Admitted to hospital prior to surgery	17 (6.6)	4 (6.3)	13 (6.8)	0.99

Categorical variables are presented as n (%). Continuous variables are presented as mean ± SD.
ciNPT, closed incision negative pressure therapy; ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus, CKD, chronic kidney disease, CAD, coronary artery disease; MI, myocardial infarction; VTE, venous thromboembolism; TPN, total parenteral nutrition; MRSA, methicillin resistant *Staphylococcus aureus*

Table 3: Oncologic and Surgical Details

Factor	All Patients (n=256)	ciNPT Dressing (n=64)	Standard Dressing (n=192)	P value
Surgery Length (minutes)	220.0 [145.0, 313.0]	233.0 [136.5, 311.5]	211.0 [150.0, 313.0]	0.82
Wound Classification	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	0.74
Skin Closure				0.27
Staples	200 (78.1)	53 (82.8)	147 (76.6)	
Suture	56 (21.9)	11 (17.2)	45 (23.4)	
Surgical Procedures				
Hysterectomy				
Radical Hysterectomy	109 (42.6)	31 (48.4)	78 (40.6)	0.32
and/or en-bloc resection)	71 (27.7)	15 (23.4)	56 (29.2)	0.34
Small bowel surgery				
Large bowel surgery	38 (14.8)	12 (18.8)	26 (13.5)	0.33
Ileostomy	68 (26.6)	18 (28.1)	50 (26.0)	0.79
Colostomy	14 (5.5)	3 (4.7)	11 (5.7)	0.99
Splenectomy	7 (2.7)	2 (3.1)	5 (2.6)	0.99
Pelvic LND	18 (7.0)	3 (4.7)	15 (7.8)	0.57
PA LND	72 (28.1)	20 (31.3)	52 (27.1)	0.57
	58 (22.7)	13 (20.3)	45 (23.4)	0.57
Emergent Surgery	7 (2.7)	3 (4.7)	4 (2.1)	0.37
Site of Cancer				0.06
Cervix	7 (2.7)	2 (3.1)	5 (2.6)	
Ovary/Fallopia	166 (64.8)	33 (51.6)	133 (69.6)	
Tube/Peritoneum				
Uterus	62 (24.2)	17 (26.6)	45 (23.6)	
Postoperative Benign	16 (6.3)	8 (12.5)	8 (4.2)	
Pathology				
Stage of Disease				0.46
I	56 (24.3)	17 (29.8)	39 (22.5)	
II	11 (4.8)	4 (7.0)	7 (4.0)	
III	114 (49.60)	24 (42.1)	90 (52.0)	
IV	49 (21.3)	12 (21.1)	37 (21.4)	
Neoadjuvant Chemotherapy	58 (27.9)	14 (27.5)	44 (28.0)	0.94
Post-operative Radiation	24 (9.4)	7 (10.9)	17 (8.9)	0.45

Categorical variables are presented as n (%). Continuous variables are presented as mean ± SD.
ciNPT, closed incision negative pressure therapy; LND, lymphadenectomy

Table 4: Infectious and Post-operative Outcomes

Factor	All Patients (n=256)	ciNPT Dressing (n=64)	Standard Dressing (n=192)	P value
Any Adverse Wound Outcome	91 (35.5)	13 (20.3)	77 (40.1)	**<0.001**
Adverse Wound Outcomes				
Superficial Incisional SSI	63 (24.6)	6 (9.4)	57 (29.7)	**<0.001**
Deep incisional SSI	13 (5.1)	0 (0.0)	13 (6.8)	**0.04**
Deep space/organ infection	9 (3.5)	0 (0.0)	9 (4.7)	0.12
Wound Dehiscence	37 (14.5)	5 (7.8)	32 (16.7)	0.07
Seroma	16 (6.3)	3 (4.7)	13 (6.8)	0.77
Hematoma	6 (2.3)	3 (4.7)	3 (1.6)	0.15
Need for wound exploration	40 (15.6)	4 (6.3)	36 (18.8)	**0.02**
Adverse Outcomes				
Re-operation	10 (3.9)	2 (3.1)	8 (4.2)	0.99
Readmission	45 (17.6)	11 (17.2)	34 (17.7)	0.89
ICU admission	40 (15.6)	10 (15.6)	30 (15.6)	0.96
Urinary Tract Infection	21 (8.2)	2 (3.1)	19 (9.9)	0.08
Pneumonia	2 (0.8)	0 (0.0)	2 (1.0)	0.99
Anastomotic Leak	6 (2.3)	3 (4.7)	3 (1.6)	0.17

Categorical variables are presented as n (%). Continuous variables are presented as mean ± SD.
ciNPT, closed incision negative pressure therapy; SSI, surgical site infection; ICU, intensive care unit

Table 5: Univariate Analysis for Surgical Site Infection

Factor	Total (N=256)	No SSI (n=193)	Superficial Incisional SSI (n=63)	p-value
Dressing Type				***<0.001***
ciNPT	64 (25.0)	58 (90.6)	6 (9.4)	
Control dressing	192 (75.0)	135 (70.3)	57 (29.7)	
Age at Surgery	60.4 ± 11.8	59.6 ± 12.0	63.0 ± 10.7	**0.04**
BMI <30 31-40 41-50 >51	65 (25.4) 112 (43.8) 71 (27.7) 8 (3.2)	52 (26.9) 86 (44.6) 50 (25.9) 5 (2.6)	13 (20.6) 26 (41.3) 21 (33.3) 3 (4.8)	0.46
ASA combined				***<0.001***
1/2	68 (26.6)	62 (32.1)	6 (9.5)	
3/4	188 (73.4)	131 (67.9)	57 (90.5)	
HTN	136 (53.1)	103 (53.4)	33 (24.3)	0.92
DM	100 (39.0)	71 (36.8)	29 (29.0)	0.18
HLD	32 (12.5)	28 (14.5)	4 (12.5)	0.09
VTE	36 (14.1)	23 (11.9)	13 (36.1)	0.08

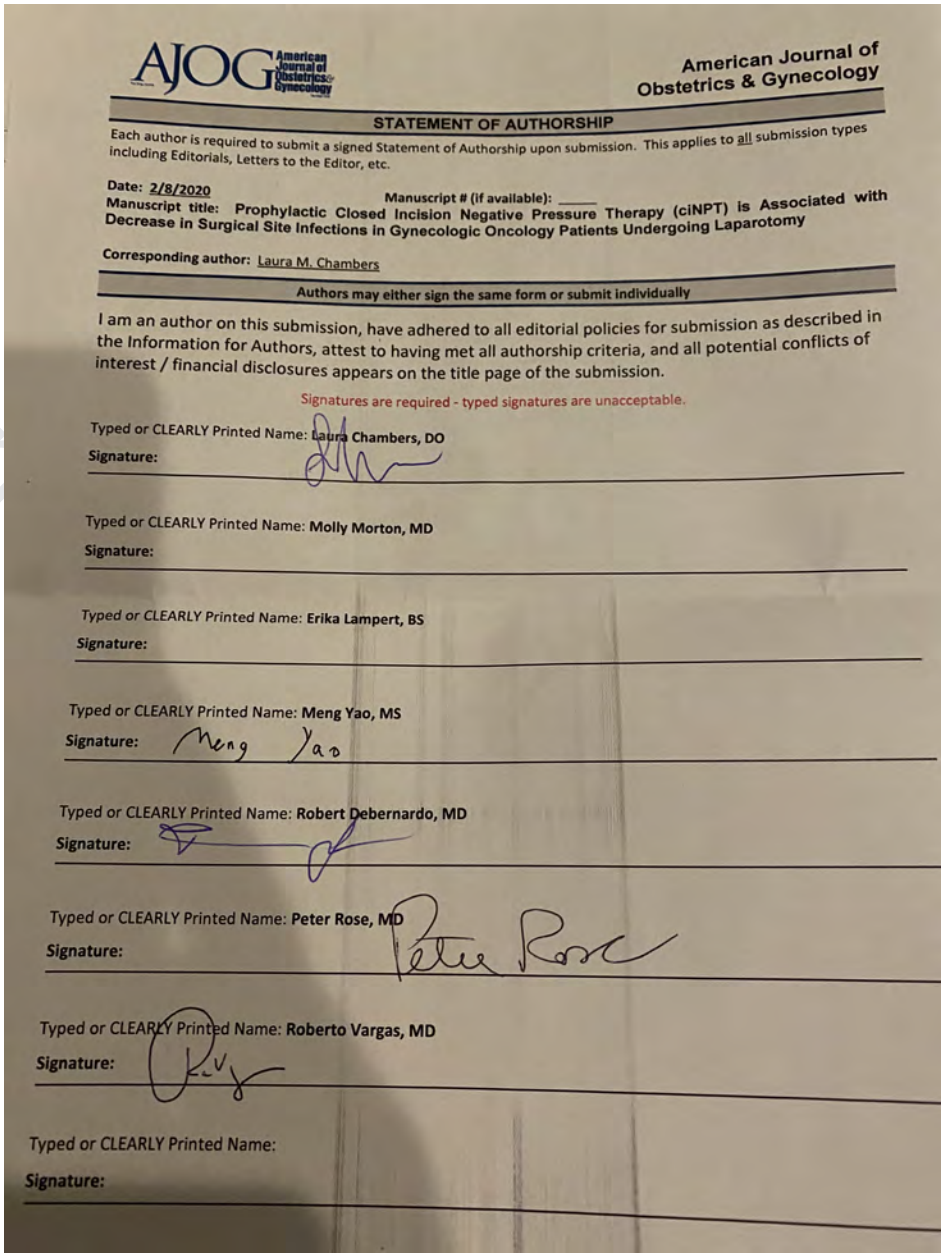
Categorical variables are presented as n (%). Continuous variables are presented as mean ± SD.

SSI, Surgical site infection; ciNPT, closed incision negative pressure therapy; BMI, body mass index; ASA, American Society of Anesthestiologists; HTN, hypertension; DM, diabetes mellitus; HLD, hyperlipidemia; VTE, venous thromboembolism

Table 6: Multivariable Analysis for Surgical Site Infection

Factor	OR (95% CI)	P Value
Superficial Incisional SSI		
ciNPT dressing	0.29 (0.12, 0.73)	**0.008**
ASA Class 3/4 vs. 1/2	3.8 (1.5,9.5)	**0.004**
Superficial Incisional and Deep Incisional SSI		
ciNPT dressing	0.29 (0.12, 0.71)	**0.007**
ASA Class 3/4 vs. 1/2	3.9 (1.6, 9.7)	**0.003**

OR, odds ratio; 95% CI, confidence interval; SSI, surgical site infection; ciNPT, closed incision negative pressure therapy; ASA, American Society; SSI, surgical site infection



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