Wound Penetration of Cefazolin, Ciprofloxacin, Piperacillin, Tazobactam, and Vancomycin During Negative Pressure Wound Therapy

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Objective: Negative pressure wound therapy (NPWT) uses subatmospheric pressure as a noninvasive adjunct to treat wounds and has demonstrated clinical efficacy by accelerating healing of a variety of acute and chronic wounds. NPWT may also play a role in preventing or treating wound infections, possibly by increasing wound penetration of antibiotics. However, clinical data in patients undergoing antibiotic and NPWT treatment are limited.

Approach: To evaluate the wound penetration of antibiotics in NPWT patients, we conducted a prospective, observational study of burn and trauma patients treated with NPWT and systemic antibiotics. We evaluated the plasma pharmacokinetic profile of systemic vancomycin, ciprofloxacin, cefazolin, and piperacillin/tazobactam, as well as total and unbound antibiotic concentrations in wound exudate from the same patients.

Results: Data from 32 patients with 37 wounds undergoing NPWT demonstrated that vancomycin, ciprofloxacin, and piperacillin/tazobactam all penetrated wounds with exudate to plasma concentration ratios more than 0.8. Cefazolin did not penetrate wounds in patients undergoing NPWT as effectively, with an average exudate to plasma concentration ratio of 0.51.

Innovation: Clinical data on the wound penetration of antibiotics in patients undergoing NPWT are limited, but these data suggest that antibiotics have different capacities for wound penetration during NPWT that should be considered when making clinical decisions.

Conclusion: This initial report suggests that (1) vancomycin, ciprofloxacin, and piperacillin/tazobactam effectively penetrate wounds during NPWT and (2) cefazolin as well as other antibiotics may not penetrate wounds during NPWT.

Keywords: antibiotic, burn, exudate, pharmacokinetics, trauma, WoundVac

INTRODUCTION

VACUUM-ASSISTED CLOSURE, or negative pressure wound therapy (NPWT), uses subatmospheric pressure as a noninvasive adjuvant ther-

apy to treat wounds. NPWT has shown clinical benefit for a variety of acute and chronic wounds,¹⁻³ especially complex wounds.⁴ In addition to isolating the wound environment and stabilizing osmotic gradients through the evacuation of fluid with accompanying electrolytes and proteins,^{5,6}

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NPWT has been shown to reduce healing time through macrodeformation (pulling the wound edges closer together) and microdeformation (pulling the interior, cellular surfaces together within the open-pore foam), resulting in the modulation of inflammation and a variety of cellular responses that stimulate angiogenesis and the formation of new granulation tissue.⁶ With the increasing prevalence of complex wounds⁴ and the efficacy of NPWT in promoting wound healing,⁶ the use of NPWT is becoming increasingly common.³

An additional benefit of NPWT may be an overall decrease in the bacterial burden in the wound bed, but the effect of NPWT on bioburden remains controversial.⁷ Furthermore, the hypothesized mechanisms responsible for any potential reduction remain unclear. Evidence has shown a reduction in counts of Gram-negative bacilli with NPWT compared with conventional wet-to-dry dressings,⁸ but reductions in Gram-positive bacilli, such as *Staphylococcus aureus*, are not consistently observed^{8,9} and highlight the need for studies on the relationship between NPWT and wound infections. NPWT produces changes in localized blood flow, tissue oxygenation and inflammation, and directly removes pathogens through vacuum pressure,^{10–12} all of which have been suggested to play a role in the overall reduction in bacterial load during NPWT⁴ but may also impact the pharmacokinetics or pharmacodynamics of drugs at or near wounds, especially antibiotics.

CLINICAL PROBLEM ADDRESSED

The efficacy of systemic antibiotics is limited by the extent to which free, unbound drug can interact with the targeted microbe in the target tissue, requiring that systemic antibiotics penetrate across tissue membranes to be effective against soft tissue infections. The impact of different wound management techniques on the effective delivery of antibiotics to the target wound site, such as the effect of blood flow changes from NPWT, has not been thoroughly examined. Patients with diabetes mellitus often have reduced circulation, are at increased risk for postoperative wound infections despite aggressive perioperative antibiotic therapy, and show reduced wound penetration of vancomycin.¹³ However, few studies have directly examined wound penetration of antibiotics during NPWT. Recently, a small preclinical study showed no difference in the penetration of cefazolin into wounds in patients treated with NPWT or non-adherent dressings.¹⁴ A small clinical study of eight patients undergoing NPWT demonstrated that vancomycin effectively penetrates a variety of

wounds in a variety of anatomic locations,¹⁵ with values exceeding those seen in patients not undergoing NPWT¹³; although this is presently the only clinical study to evaluate antibiotic penetration during NPWT, the small, heterogeneous nature of the patient population and limited data highlight the need for more information on wound penetration of antibiotics in patients undergoing NPWT. In this study, we evaluated the pharmacokinetic profile and wound penetration of vancomycin, ciprofloxacin, cefazolin, piperacillin, and tazobactam in 32 patients undergoing NPWT for acute, complex wounds.

MATERIALS AND METHODS

Patients

After obtaining approval from the Institutional Review Board, patient consent was obtained for enrollment in a prospective, observational clinical trial. Hospitalized adult patients ≥ 18 years old were eligible for this study if they met the following inclusion criteria: presence of an NPWT device on a wound or incision from which liquid exudate could be recovered and receiving an antibiotic approved in the study. Notably, infection was not a requirement of the study to accommodate inclusion of postoperative NPWT use in conjunction with perioperative antibiotics, or empiric antibiotic therapy. Wound area was estimated by external dimensions as the length times width measured in centimeters. Body weight was the value reported in the patient's medical record on the day of sample collection.

Sample collection

The KCI InfoV.A.C. system (Kinetic Concepts, San Antonio, TX) was used as the NPWT device according to hospital practice. To facilitate recovery of liquid wound exudate, empty canisters lacking congealing agent ("study" canisters, KCI catalog #M827507) were used during the plasma collection period in place of the standard canister containing congealing agent. The study canister was inserted into the NPWT device at the start of plasma sampling, immediately before antibiotic administration. Wound exudate was collected using intermittent negative pressure of -125 mmHg throughout the plasma sampling interval, at the end of which the study canister was replaced with a standard clinical-use canister. The study canister containing wound exudate was frozen at -80°C until analysis.

The plasma sampling interval was determined by the antibiotic dosing interval. For dosing every 6 h (piperacillin/tazobactam), blood samples were collected at 0 (predose), 0.5, 2, 4, and 6 h. For dosing

every 8 h (cefazolin, vancomycin), blood samples were collected at 0 (predose), 0.5, 2, 4, and 8 h. For dosing every 12 h (vancomycin, ciprofloxacin), blood samples were collected at 0 (predose), 0.5, 2, 4, 8, and 12 h. Blood samples were immediately centrifuged at $1,000\times g$ for 10 min, and the plasma was aliquoted into separate tubes and frozen at -80°C until analysis. Wound exudate was collected throughout the 6-, 8-, or 12-h blood sampling period and the entire sample was used for analysis.

Sample preparation

Total drug concentrations in plasma were determined using solid phase extraction (SPE) and high-performance liquid chromatography (HPLC). In each case, an internal standard was added to 200 μL of sample and the sample was drawn by vacuum through SPE cartridges (Oasis HLB; Waters, Milford, MA) preconditioned with methanol. Cartridges were then equilibrated with wash solution (for piperacillin/tazobactam, 0.067 M phosphate buffer, pH 7.4; for cefazolin and vancomycin, deionized water; for ciprofloxacin, deionized water, pH 3.1 with hydrochloric acid) and rinsed before sample elution with acetonitrile (for piperacillin/tazobactam, cefazolin, vancomycin) or methanol (for ciprofloxacin). The eluent was evaporated under air and reconstituted in 200 μL of the aqueous component of the HPLC mobile phase (0.1 M phosphate buffer, pH 3.0). Plasma levels for piperacillin and tazobactam were analyzed using oxacillin as an internal standard,¹⁶ for cefazolin using vancomycin as an internal standard, for vancomycin using cefazolin as an internal standard, and for ciprofloxacin using levofloxacin as an internal standard. Free (unbound) drug concentrations in plasma were determined for each drug using centrifugal ultrafiltration¹⁷ with Centrifree UF filters (30 kD; Millipore, Billerica, MA) loaded with sample and centrifuged at $1,500\times g$ for 30 min. Appreciable binding of drug to filters was not detected.

Total and free drug concentrations in wound exudate were determined using the same SPE and HPLC methods as for plasma. Based on pilot testing and prior studies of biomarkers in wound exudate,^{18–20} proteins were precipitated before SPE to increase recovery in the total drug measurement samples: for piperacillin/tazobactam, cefazolin, and vancomycin, 800 μL methanol was added to 200 μL exudate; for ciprofloxacin, 1 mL acetonitrile was added to 200 μL exudate before centrifugation (4°C , 10 min, $1,000\times g$). After centrifugation, the supernatant was evaporated under air and reconstituted in 1 mL deionized water before SPE.

HPLC analysis

HPLC analysis was conducted as described previously.¹⁶ Samples were analyzed with a Dionex 3000 HPLC system (Thermo-Fisher, Sunnyvale, CA). Stationary phase columns (Phenomenex, Torrance, CA) used were C18 (Kinetix) for piperacillin and tazobactam, C8 (Luna) for vancomycin and cefazolin, and C18 (Luna) for ciprofloxacin. Mobile phases used were 0.1 M phosphate buffer (pH 3.0) for piperacillin (isocratic) and tazobactam (linear gradient from 5% to 50% acetonitrile over 10 min); 5 mM phosphate buffer (pH 2.8) for vancomycin and cefazolin (linear gradient from 97% to 80% phosphate buffer over 11.5 min); 0.1% trifluoroacetic acid (TFA) and acetonitrile for ciprofloxacin (linear gradient from 18% to 20% TFA over 10 min). Mobile phase flow rate was 1 mL/min for piperacillin, tazobactam, and ciprofloxacin, and 1.5 mL/min for cefazolin and vancomycin. Ciprofloxacin was detected using fluorescence (280 nm excitation, 450 nm emission), and all other analytes were detected by UV at 210 nm.

Separate calibration curves were constructed for the exudate and plasma samples and processed in parallel with the samples using antibiotic-spiked pseudoexudate or donated human plasma to determine drug concentrations in plasma or exudate. Free drug calibration curves were constructed by diluting known amounts of each analyte in phosphate-buffered saline to make five to seven calibration standards across a range of concentrations. Total drug calibration curves were constructed by addition of known amounts of each analyte to donated human plasma (Biological Specialty Corporation, Colmar, PA) at five to seven concentrations prepared and processed by SPE in tandem with test samples. Standards confirmed a linear response between analyte and internal standard peak ratios and analyte concentration. Known validation standards were used to monitor accuracy between calibration runs.

Statistical analysis

For comparison of wound penetration, the percentage of free drug (in plasma or effluent) was defined as the concentration of free drug divided by the concentration of total drug. The average plasma concentration (C_{plasma}) was calculated using pharmacokinetic software (Phoenix WinNonLin; Certara, Princeton, NJ), determined as the area under the curve divided by the dose interval (τ). Continuous variables were analyzed using Student's *t*-test or Wilcoxon signed-rank test for two groups, based on the results of the Shapiro-Wilks test of normality, or one-way ANOVA, with

Tukey–Kramer *post hoc*, or Kruskal–Wallis for multiple groups. Variables that passed or failed the test for normality are presented as mean ($\pm$ standard deviation) or median (interquartile range), respectively. Categorical variables were compared using Chi-squared, Mann–Whitney, or Fisher’s exact tests, as appropriate. Grubbs’ test was used to determine whether an outlier was present in the cefazolin data. Statistical significance was accepted at $p < 0.05$. All data were analyzed using SAS 9.1 (SAS, Cary, NC).

RESULTS

A total of 32 patients were enrolled and administered vancomycin (7 patients), ciprofloxacin (7 patients), cefazolin (8 patients), or piperacillin/tazobactam (10 patients); 5 patients had injuries to 2 sites each, so a total of 37 sites with NPWT were

evaluated in this study (8, 9, 9, and 11 sites for vancomycin, ciprofloxacin, cefazolin, and piperacillin/tazobactam, respectively). Demographic and injury data are shown in Table 1. Patients were 42.5 ± 16.6 years old, weighed 99.1 ± 20.9 kg, and had injuries 109.6 ± 90.1 cm² in size, 73% of which were to an extremity and 22% of which were to the torso. Patients were 78% male, and 7 of the 37 injuries (19%) were received in combat. Sample collection began 6.3 ± 3.8 days postinjury and patients were discharged 23.9 ± 15.2 days postinjury. Treatment groups did not differ with respect to age, weight, injury size, time from injury to sample collection, or time from injury to hospital discharge. No significant differences in pharmacokinetic parameters, effluent rate, or wound penetrance of antibiotics were noted with respect to mechanism of injury.

Antibiotic concentrations in exudate from a total of 37 NPWT sites were analyzed and compared

Table 1. Clinical characteristics of subjects examined in this study

Patient No.	Age	Sex	Weight (kg)	Injury Information/Location	Injury Size (cm ²)	Combat Injury	Time to Sample Collection (Days)	Time to Discharge (Days)	Antibiotic
1	55	M	77.1	ODRI (MRSA), knee	24	No	7	8	Vancomycin
6	45	M	95.1	MVC, R calcaneus	224	No	3	32	Vancomycin
12	48	M	86.9	MCC, L calcaneus	200	No	6	13	Vancomycin
26	28	M	78.6	IED, L ankle, amputation	20	Yes	14	39	Vancomycin
26	28	M	78.6	IED, R leg, shrapnel	120	Yes	14	39	Vancomycin
34	32	M	84.5	MCC and burn, R forearm, skin graft	91	No	3	15	Vancomycin
42	26	M	144.4	MVC, L upper arm	80	No	14	19	Vancomycin
46	67	M	90.5	Burn, L lower leg	416	No	3	14	Vancomycin
36	33	M	136.1	GSW, lateral leg	189	No	15	27	Ciprofloxacin
36	33	M	136.1	GSW, medial leg	396	No	15	27	Ciprofloxacin
41	35	M	90.8	IED, L knee/elbow	119	Yes	12	41	Ciprofloxacin
41	35	M	90.8	IED, R popliteal fossa	30	Yes	12	41	Ciprofloxacin
43	41	F	76.4	MVC, laparotomy incision	64	No	11	58	Ciprofloxacin
53	31	M	75.6	MVC, L foot, fracture/ulcer	6	No	5	63	Ciprofloxacin
58	68	M	86.4	ODRI, R malleolus	1	No	2	3	Ciprofloxacin
59	55	F	181.4	Diabetic amputation, L foot	44	No	7	13	Ciprofloxacin
60	62	F	131.8	Total colectomy, cancer	112	No	6	17	Ciprofloxacin
11	36	M	68.0	Penetrating trauma (fall), R leg	130	No	2	5	Cefazolin
15	43	M	104.1	Blunt trauma (fall), R ankle	24	No	2	14	Cefazolin
18	28	M	101.5	IED, R upper arm,	320	Yes	6	22	Cefazolin
18	28	M	101.5	IED, R lower arm,	320	Yes	6	22	Cefazolin
22	36	M	99.2	Blunt trauma (fall), R leg, AKA	32	Yes	2	10	Cefazolin
23	33	M	106.9	Penetrating trauma (stab), R forearm	24	No	7	9	Cefazolin
24	29	M	74.8	Crush (accident), L leg	126	No	2	10	Cefazolin
27	57	F	110.0	MCC, L leg	10	No	5	11	Cefazolin
30	29	M	110.7	MCC, L leg, amputation	20	No	3	18	Cefazolin
2	50	M	103.4	MCC, L arm amputation	204	No	7	16	Pip/Tazo
2	50	M	103.4	MCC, abdomen	308	No	7	16	Pip/Tazo
7	25	F	72.9	Pelvic inflammatory disease	68	No	4	32	Pip/Tazo
10	83	F	75.7	MVC, abdomen	105	No	4	31	Pip/Tazo
14	66	M	109.1	Subtalar fusion, R ankle	8	No	5	21	Pip/Tazo
17	24	F	100	MVC, ankle, laceration	91	No	3	14	Pip/Tazo
21	25	M	111.9	MCC, abdomen,	73	No	4	68	Pip/Tazo
25	26	M	100	Multiple GSW, abdomen	78	No	3	20	Pip/Tazo
28	63	M	107.1	Fibular graft donor site, R leg	119	No	12	23	Pip/Tazo
33	83	M	86	Ischemic bowel resection	85	No	4	28	Pip/Tazo
37	55	M	87.1	ORIF, thigh	33	No	2	7	Pip/Tazo

AKA, above the knee amputation; GSW, gunshot wound; IED, improvised explosive device; MCC, motorcycle crash; MRSA, methocillin-resistant staphylococcus aureus; MVC, motor vehicle crash; ODRI, orthopedic device-related infection; ORIF, open reduction/internal fixation; Pip/Tazo, piperacillin/tazobactam.

with plasma pharmacokinetic data. To determine whether antibiotics penetrate wounds in patients undergoing NPWT, the average total plasma (C_{plasma}) and wound exudate (C_{exudate}) concentrations of vancomycin, ciprofloxacin, cefazolin, piperacillin, and tazobactam were compared. The ratio of wound exudate concentration to average plasma concentration ($C_{\text{exudate}}:C_{\text{plasma}}$) was determined to be 1.86 ± 0.70 for vancomycin, 0.84 ± 0.37 for ciprofloxacin, 0.92 ± 0.32 for piperacillin, 1.09 ± 0.54 for tazobactam, and 0.81 ± 0.92 for cefazolin; after removal of one outlier (Grubbs' $Z=2.6$, critical $Z=2.2$), the ratio for cefazolin was 0.51 ± 0.22 (Fig. 1B). The percentage of the total drug that was free (unbound) was higher in wound exudate than plasma for ciprofloxacin ($76.4\% \pm 29.4\%$ vs. $41.9\% \pm 9.9\%$, respectively; $p < 0.01$) and cefazolin ($55.4\% \pm 23.2\%$ vs. $13.6\% \pm 6.9\%$, respectively; $p < 0.001$), but not for vancomycin ($45.3\% \pm 19.6\%$ vs. $37.2\% \pm 10.6\%$), piperacillin ($55.5\% \pm 21.1\%$ vs. $57.3\% \pm 12.5\%$),

or tazobactam ($56.8\% \pm 26.8\%$ vs. $59.2\% \pm 23.8\%$) (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/wound).

DISCUSSION

In this study, we show that vancomycin, ciprofloxacin, piperacillin, and tazobactam penetrated wounds in patients undergoing NPWT with concentrations in the wound exudate reaching at least 80% of the average steady-state plasma concentration ($C_{\text{exudate}}:C_{\text{plasma}} \geq 0.8$). Although cefazolin also produced exudate concentrations at least 80%, on average, of those in plasma, the variability from one outlier in the data reduces confidence in concluding that cefazolin effectively penetrates all wounds in patients undergoing NPWT. After removal of one outlier, cefazolin only achieved a $C_{\text{exudate}}:C_{\text{plasma}}$ ratio of 0.51, which is at least 40% lower than the ratios achieved by all the other antibiotics tested in this study. Cefazolin as well as other antibiotics may not penetrate wounds in patients undergoing NPWT because of the high protein binding of cefazolin²¹ relative to the other antibiotics observed in this study.^{22–26} Notably, other pharmacokinetic and pharmacodynamic variables, such as elimination half-life, were in agreement with previously established values (Supplementary Table S1).^{16,27–30}

Vancomycin, ciprofloxacin, cefazolin, and piperacillin/tazobactam are commonly used for their efficacy against aerobic and anaerobic Gram-positive bacteria or broad spectrum activity. Antibiotic efficacy is limited, in part, by the extent to which free, unbound drug can interact with the targeted microbe in the target tissue, which can be complicated by limited antibiotic penetration across membrane barriers. Minimum inhibitory concentrations are often used to guide antibiotic selection and estimate the dose necessary to achieve the desired range of systemic concentrations in the blood. Studies have examined antibiotic concentrations in interstitial fluid to determine the extent of penetration.¹³ However, few studies have investigated the effect of NPWT on antibiotic wound penetration.

A small, preclinical study concluded that NPWT had no effect on the penetration of cefazolin, with tissue homogenate to plasma ratios of 0.39–0.54 and 0.33–0.50 for NPWT and conventional dressing treatments, respectively.¹⁴ In contrast, a small clinical study of eight patients concluded that NPWT significantly increases vancomycin wound penetration¹⁵ with wound exudate to plasma ratios of 0.67 ± 0.19 compared with data from a different non-NPWT study showing an interstitial fluid to

Figure 1. Wound penetrance of antibiotics during NPWT. (A) C_{plasma} = average plasma concentration, C_{exudate} = exudate concentration. (B) Ratio of $C_{\text{plasma}}:C_{\text{exudate}}$. Cefazolin* = cefazolin data after outlier removal. NPWT, negative pressure wound therapy.

plasma ratio of 0.3 in normal subjects.¹³ However, the non-NPWT data were obtained from interstitial fluid using microdialysis,¹³ a technique that measures only unbound drug. In this study and reported elsewhere,²⁵ vancomycin was found to be ~40% protein bound. After adjusting the microdialysis data for protein binding, the wound penetration ratio for total vancomycin would be ~0.5 in non-NPWT patients, which generally agrees with the wound exudate to plasma ratio of 0.67 ± 0.19 previously reported during NPWT patients,¹⁵ suggesting that NPWT does not affect the penetration of vancomycin.

Although it is not clear whether the previous NPWT study evaluating wound penetration of vancomycin examined free or total vancomycin concentration,¹⁵ the present data show substantially higher wound penetration of vancomycin, with a wound exudate to plasma ratio of 1.86 ± 0.70 . The patients in this study showed higher clearance of vancomycin (8.2 ± 2.9 L/h; Supplementary Table S1) than those in the previous study (4.2 ± 2.4 L/h)¹⁵ but overlapping average serum/plasma concentration ranges (15.8 ± 6.2 μ g/mL vs. 34.5 ± 33.2 μ g/mL), so higher blood concentrations driving a nonlinear wound penetration would not explain the higher wound exudate to plasma ratios observed. It is possible that a difference in weight-normalized data, exudate rate, sample collection, and analysis times could account for some of the observed difference, as vancomycin stability was only validated for 24 h, but patient weights and information on the exudate rate were not provided previously.¹⁵ Differences in the sample analysis method (fluorescent polarization immunoassay vs. HPLC) could have accounted for some of the discrepancy, although the extent of that difference is unclear. Regardless of the differences in wound exudate concentrations reported here and previously,¹⁵ it is clear that vancomycin effectively penetrates wounds in patients undergoing NPWT, possibly to a greater extent than normal tissue. More data are needed to determine the true extent of vancomycin penetration during NPWT to allow for the calculation of more accurate plasma concentration targets.

This study has several limitations. Despite having a total of 37 NPWT sites from 32 patients, we evaluated several different antibiotics in this study, and data for each were obtained from 8 to 11 NPWT sites. As with many clinical observational studies, the patient population in our study was diverse: patient ages ranged from 24 to 83 years, weight ranged from 68 to 181 kg, combat and non-combat injuries were included, and the time from

injury to sample collection varied as well. Furthermore, the injury size, location, and exudate rate varied widely, with no statistical correlations in antibiotic penetration. As investigations into antibiotic wound penetration are just beginning, the relationship between established pharmacokinetic and pharmacodynamic parameters, which predict optimal cure of infection in the bloodstream, and wound antibiotic content is unknown. Specifically, static single-concentration characterization of wound exudate antibiotic concentration does not capture dynamic concentration changes in the wound. Thus, in this study we cannot relate the relevant pharmacokinetic and pharmacodynamic parameters for the antibiotics studied here (such as time more than minimum inhibitory concentration [MIC], or area under the curve to MIC ratio) to optimal values associated with clearance of wound infection. Future studies should attempt to capture dynamic changes of wound antibiotic concentrations over time and determine whether wound location, size, or severity affects the antibiotic penetration during NPWT. Owing to these limitations, restraint must be exercised in applying broad clinical recommendations with confidence before additional data are obtained. Future studies should also investigate the use of NPWT with instillation, as it is unclear what effect topical application of additional fluid, with or without antibiotics, in conjunction with NPWT would have on antibiotic wound penetrance.

Concerns have been raised about the effect of alterations in localized blood flow during NPWT on drug distribution.^{4,10–12} Previous work has shown that vancomycin effectively penetrates wounds in patients undergoing NPWT, possibly to a greater extent than in normal tissue.¹⁵ These data add to this existing literature and extend it further by showing that vancomycin, ciprofloxacin, piperacillin, and tazobactam all penetrate wounds in patients undergoing NPWT, and suggest that ceftazolin may not penetrate wounds as effectively under the NPWT conditions studied here. Controlled studies are needed to increase the available data and strengthen conclusions and clinical recommendations to increase the accuracy of pharmacokinetic dosing of antibiotics for patients undergoing NPWT.

INNOVATION

Data on the wound penetration of antibiotics during NPWT are extremely limited. A preclinical study concluded that NPWT had no effect on the penetration of ceftazolin, whereas a small clinical

study concluded that NPWT significantly increases the penetration of vancomycin. More data are needed to properly inform clinicians during antibiotic selection. This study evaluated the penetrance of several common antibiotics and identified a differential capacity for wound penetration of antibiotics during NPWT. Notably, vancomycin, ciprofloxacin, piperacillin, and tazobactam efficiently penetrated wounds during NPWT, whereas cefazolin was significantly less efficient. Future studies are needed to extend these novel findings, but these early results suggest that cefazolin may be a less effective antibiotic in some NPWT situations than other agents such as vancomycin, ciprofloxacin, piperacillin, and tazobactam that have better wound penetrance.

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DISCLAIMER

The opinions or assertions contained herein are the private views of the authors and are not to be

KEY FINDINGS

- Vancomycin, ciprofloxacin, and piperacillin/tazobactam effectively penetrate wounds during NPWT.
- Cefazolin may not penetrate wounds as effectively during NPWT.
- Wound penetrance of antibiotics should be considered in patients undergoing NPWT.

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AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist for any of the authors. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

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Abbreviations and Acronyms

C_{plasma}	= average plasma concentration
HPLC	= high-performance liquid chromatography
NPWT	= negative pressure wound therapy
ODRI	= orthopedic device-related infection
SPE	= solid phase extraction