Pressure Ulcer Development and Vasopressor Agents in Adult Critical Care Patients: A Literature Review

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Abstract
Critical care units provide technologically sophisticated care to the sickest patients in the healthcare system. The contribution of iatrogenic factors, including administration of pharmacologic agents such as vasopressors, to pressure ulcer (PU) development in adult critical care patients is understudied, thus less understood, but may be an important PU risk factor to consider in the critical care population. Vasopressor agents are potent vasoconstrictors commonly administered to critical care patients to elevate mean arterial pressure to counteract the effects of inadequate tissue perfusion and hypoxia; they have reemerged over the past decade in contemporary intensive care units as important first-line drugs in the treatment of shock states. A comprehensive review of the literature was undertaken in order to determine the level of evidence regarding the relationship between vasopressor agents (norepinephrine, epinephrine, phenylephrine, vasopressin, and dopamine) and PU development in adult critical care patients. Computerized databases of EBSCO-CINAHL and OVID MEDLINE were searched for English-language publications from 2000 to the present using the following terms: pressure ulcer, vasopressor, norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine, critical care and pressure ulcers; intensive care and pressure ulcers; and pressure ulcer risk factors. Ten studies were identified that met the inclusion/exclusion criteria. Statistically significant associations were reported between the broad category of vasopressor agents and PU development in seven studies. Of those, two identified a specific vasopressor agent (norepinephrine) as a significant predictor of PU development in this population. Empirical support for the broad category of vasopressors as a PU risk factor is increasing, and a small body of evidence is emerging to support the role of one specific vasopressor (norepinephrine) in PU development. Increased vigilance regarding PU risk in critical care patients receiving vasopressor agents may be warranted. However, studies are needed to examine the effects of individual vasopressor agents and dosage and duration thresholds, as well as empirical investigation regarding the synergistic effect of multiple vasopressor agents administered simultaneously, on PU development in this population. Finally, research is needed to further elucidate vasopressor use as an independent risk factor for PU development in this population.

Keywords: literature review, pressure ulcer, intensive care, risk factors, vasopressins

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Potential Conflicts of Interest: none disclosed

Intensive care units (ICUs), also known as critical care units, provide highly complex care to the most critically ill patients in the healthcare system. The development of a pressure ulcer (PU) in a critical care patient confers substantial physiologic stress on someone already severely compromised, increasing the risk for hospital-acquired infection, prolonged hospitalization, and mortality. Despite the implementation of evidence-based clinical practice guidelines and advances in technology, the prevalence of hospital-acquired PUs continues to be a major healthcare concern. The 2011 HealthGrades Patient Safety in American Hospitals study cited PU occurrence as the second most common adverse patient safety event in hospitalized patients, with attributable healthcare costs estimated at $1.99 billion. Because PU rates in the ICU setting are cited as the highest among hospitalized patients, ranging from 14% to 42%, it is evident the struggle to prevent PUs has not been completely successful in this population. In a 2009 prevalence study, 3.3% of critical care patients were found to have developed severe hospital-acquired PU, defined as a Stage III or Stage IV PU, unstageable PU, or sus-
pected deep tissue injury (sDTI).8

Determination of PU risk has been described as both complex and multifactorial.9 A plethora of risk factors has been found to be associated with PU development in critical care patients, such as factors measured by the Braden Scale (altered mobility,10,11 altered sensory perception,12,13 exposure to moisture,10,13 and friction/shear11,13). In addition, advanced age,7,10,11,14–16 prolonged ICU length of stay,7,10–14 emergent admission to the ICU,16–18 severity of illness measured via the APACHE II scale,7,11,19 compromised nutritional status,19 and comorbid conditions including diabetes mellitus, infection, and cardiovascular/vascular disease11,14,15,18,20 all have been associated with PU development in critical care patients. The wide variability of PU risk factors experienced by critical care patients demonstrates the multi-etiologic nature of PU development in this population; however, it also reveals a clear lack of consensus regarding risk factors that pose the greatest threat to this population, a conclusion corroborated by two systematic reviews in the critical care literature.6,21

The unique contribution of iatrogenic factors such as the administration of pharmacologic agents, especially vasopressors, to PU development must be considered in the critical care population. Commonly used vasopressor agents (norepinephrine, epinephrine, vasopressin, phenylephrine, and dopamine) are potent drugs that induce vasoconstriction for the purpose of elevating mean arterial pressure (MAP) in critically ill patients to counteract the effects of inadequate tissue perfusion and hypoxia.22,23 Although vasopressor agents are not new treatment modalities (there is evidence of their use in medicine more than a century ago),24 in the past decade these agents have reemerged in contemporary ICUs as important first-line drugs, commonly administered to critically ill patients in shock states.25

The pharmacodynamic properties inherent in these drugs suggest these agents may play a role in altering tissue perfusion over bony prominences and lead to PU development. However, a dearth of evidence currently exists to support this relationship, suggesting the role of vasopressor agents in PU development is understudied and thus less understood. While current critical care practice guidelines identify vasopressor agents as potential risk factors for PU development, they affirm the need for additional empirical study.26,27

The purpose of this review is to evaluate the current level of evidence regarding the relationship between vasopressor agents (norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine) and PU development in adult critical care patients.

Method

In order to gain a better understanding of the relationship between vasopressor agents and PU development in adult critical care patients, a comprehensive review of the literature was undertaken. The computerized databases EBSCO-CINAHL and OVID-MEDLINE were searched using the terms pressure ulcer, vasopressor, norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine, critical care and pressure ulcer; intensive care and pressure ulcer; and pressure ulcer risk factors. In addition, journal hand searching and ancestry searching were employed.

Inclusion criteria established for this review were: 1) peer-reviewed and published reports on PU risk factors in adult patients in the critical care (ICU) setting in which the variable vasopressors or any of the following were included as individual variables under investigation: norepinephrine, epinephrine, vasopressin, phenylephrine, and/or dopamine; and 2) studies conducted from 2000 to the present. Exclusion criteria were: 1) studies in languages other than English; and 2) studies in which interventions for PU prevention in ICU patients were the primary focus. Studies conducted before 2000 were excluded because standardization of vasopressor agents used in contemporary ICUs for the treatment of severe sepsis and septic shock emerged in 2001 following the landmark Rivers et al study28 and the implementation of the Surviving Sepsis Campaign clinical practice guidelines in 2001.29 Severe sepsis and septic shock account for 20% of all ICU admissions and are the leading causes of death in noncardiac ICU settings.29

Ten studies satisfied the inclusion/exclusion criteria for this review.11,14–18,30,32 Critical care settings represented in these studies included medical/surgical ICUs, ICUs, general ICUs (types not specified), and a long-stay perianesthesia care unit. A summary of these studies can be found in Table 1.

Overview of Vasopressor Agents and Receptor Activity

Vasopressors are pharmacologic agents administered intravenously to increase blood pressure by inducing arteriole vasoconstriction. They are used to treat hypotension resulting from various shock states including hypovolemic, severe

Key Points

- Vasopressor agents are commonly administered to patients in intensive care environments, and some evidence suggests their use may increase the risk of pressure ulcer (PU) development.
- Following a systematic literature search, the author found seven of the 10 studies identified reported an increased risk of PUs in patients treated with vasopressors.
- Increased vigilance regarding PU risk in critical care patients receiving vasopressor agents may be warranted until additional research has been conducted.
Table 1: Summary of critical care studies including vasopressor agents as variables under investigation (2000 to present) (chronologic order)

| Study Authors/Year | Design | Sample size/Type of ICU | Norepinephrine | Vasopressin | Dopamine | Phenylephrine | Epinephrine | Vasopres- sor agent(s) not identified in study | Other risk factors significant in multivariate analysis
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<tbody>
<tr>
<td>Theaker et al 16/2000</td>
<td>Prospective cohort</td>
<td>286/ type not specified</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>APACHE II score, fecal incontinence, anemia, length of stay</td>
</tr>
<tr>
<td>Eachempati et al 19/2001</td>
<td>Prospective cohort</td>
<td>412/surgical</td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Emergent ICU admission; days in bed, days without nutrition</td>
</tr>
<tr>
<td>Frankel et al 14/2007</td>
<td>Retrospective</td>
<td>820/surgical</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>Diabetes; spinal cord injury; age &gt;60 years; creatinine &gt;3.0mg/dL</td>
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<tr>
<td>Compton et al 17/2008</td>
<td>Prospective, epidemiologic</td>
<td>698/medical</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt; (&gt;5µ/kg/minute)</td>
<td></td>
<td></td>
<td>Male gender; moist skin; edematous skin; centralized circulation; mottled skin; reddened skin</td>
<td></td>
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<tr>
<td>Kaitani et al 18/2010</td>
<td>Prospective, cohort</td>
<td>98/ type not specified</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Emergency ICU admission; infrequent turning</td>
<td></td>
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<tr>
<td>Slowikowski and Funk 15/2010</td>
<td>Prospective/descriptive correlational</td>
<td>369/ surgical</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Age &gt;70 years; diabetes mellitus; low Braden Scale score</td>
<td></td>
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<tr>
<td>Alderdeen et al 31/2011</td>
<td>Retrospective review</td>
<td>87/ICU (type not specified)</td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Spinal cord injury; age &gt;40 years</td>
<td></td>
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<tr>
<td>Concepcion et al 30/2011</td>
<td>Prospective, pilot study</td>
<td>16/peri-anesthesia care unit</td>
<td>X&lt;sup&gt;def&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None identified</td>
<td></td>
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<tr>
<td>Cox 11/2011</td>
<td>Descriptive/correlational design—retrospective analysis</td>
<td>347/ Medical/Surgical ICU</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X&lt;sup&gt;o&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Age, longer ICU lengths of stay, cardiovascular disease, Braden mobility subscale, Braden friction/shear subscale</td>
<td></td>
</tr>
<tr>
<td>Tschannen et al 32/2012</td>
<td>Retrospective cohort</td>
<td>3,225/Surgical patients/ICU type not specified</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Low body mass index; history of diabetes; multiple surgeries during admission; total time in the operating room; Braden score on admission; mortality risk</td>
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<sup>a</sup>=not all risk factors investigated presented, only risk factors significant in multivariate analysis; <sup>b</sup>=significant in bivariate analysis; <sup>c</sup>=significant in multivariate analysis; <sup>d</sup>=non-significant finding; <sup>e</sup>=defined as variables under investigation; <sup>f</sup>=medium/high doses(≥2.5 mg/hour) of norepinephrine infusion as compared to low dose(<2.5 mg/hour); <sup>g</sup>=specific vasopressors not identified separately in the analysis.
Table 2. Overview of vasopressors agents22,23,33,49-52

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor Activity</th>
<th>Major clinical effects</th>
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<tbody>
<tr>
<td></td>
<td>Alpha(α)</td>
<td>Beta-1(β1)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>X</td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Phenylephrine</td>
<td>X</td>
<td></td>
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<tr>
<td>Dopamine</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vasopressin</td>
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</table>
Sepsis/septic shock, cardiogenic, anaphylaxis, or neurogenic etiologies. Commonly administered vasopressor agents include norepinephrine, epinephrine, phenylephrine, dopamine, and vaspressin. Vaspressors are indicated for a decrease of >30 mm Hg from baseline systolic blood pressure or mean arterial pressure <60 mm Hg.32,33,34

Most vaspressors (norepinephrine, epinephrine, phenylephrine, dopamine, and vaspressin) are classified as catecholamines or sympathomimetic agents, but the physiologic responses they exert are not identical. The pharmacokinetic properties of these drugs differ based on the various sympathetic (adrenergic) receptors stimulated. Although some agents act on multiple adrenergic receptors, the receptor effect of other agents can be dose-dependent. Stimulation of alpha (α) adrenergic receptors results in vasoconstriction, increased systemic vascular resistance (SVR), and increased MAP. Conversely, stimulation of beta-2 (β2) receptors induces vasodilation and decreases SVR. Beta 1 (β1) receptors are common in the heart and when stimulated result in increased cardiac contractility and heart rate, but they have minimal vasoconstrictive properties. Dopamine receptors present in the kidneys, mesentery, heart, and cerebral vascular beds impose a vasodilatory effect when stimulated, while other dopamine receptors induce powerful vasoconstrictive properties mediated through the release of norepinephrine.32,33

Vaspressors. Vaspressin (antidiuretic hormone) is a vasopressor that is not a sympathomimetic agent; therefore, it does not act on adrenergic receptors in the body. It is a peptide hormone capable at higher doses of inducing potent vasoconstriction through V1 receptors in the systemic, splanchnic, renal, and coronary arteries. Vaspressin is frequently used as a second-line agent and occasionally as a first-line agent in the treatment of various shock states, including septic shock and anaphylaxis.32,33,34

Vaspressin use can reduce the dosage demands of first-line vaspressors such as norepinephrine.32,33 Table 2 contains a summary of vaspressor agents and associated receptor activity and clinical effects.

A number of significant complications including hypoperfusion, dysrhythmias, myocardial ischemia, and hyperglycemia have been attributed to vaspressor use.32 The risk of these complications escalates with administration of higher doses and when hemodynamic instability necessitates simultaneous administration of multiple agents. Excessive vasoconstriction due to both hypotension and vaspressor administration can induce inadequate perfusion of the extremities, mesenteric arteries, and kidneys. Mesenteric hypoperfusion can result in shock liver, intestinal ischemia, or translocation of gut flora, leading to bactereemia; hypoperfusion in the kidneys can result in oliguria and acute renal failure. In the skin, hypoperfusion can induce dusky skin changes at the tips of the fingers and/or toes, which can progress to necrosis and result in autoamputa-

Vaspressors and PU Development: Review of the Literature

Nonsignificant relationships between vaspressor agents and PU development were reported in three of the 10 studies reviewed.15,18,19 In a prospective, correlational study of factors associated with PU development in 369 surgical intensive care patients, Slowikowski et al15 found no statistically significant relationship between the use of vaspressors and PU development. Significant risk factors in multivariate analysis in this study included age ≥70 years (OR = 2.14, P = 0.004; 95% CI, 1.27–3.62), low Braden Scale score (OR = 1.30, P = 0.19; 95% CI, 1.15–1.47), and diabetes (OR = 1.93, P = 0.004; 95% CI, 1.11–3.35). In this study, 59 (16%) of the patients were reported to have received vaspressors. Similarly, in a prospective cohort study of 412 surgical intensive care patients, Eachempati et al19 found a nonsignificant difference in univariate analysis in vaspressor use between patients who developed PUs and persons who remained PU-free. In this study sample, emergent ICU admission (OR = 36, P = 0.0001; 95% CI, 0.2290–0.7694), number of days in bed (OR = 1.05, P = 0.0064; 95% CI, 0.0013–0.0156), and three or more days without nutrition (OR = 0.51, P = 0.0014; 95% CI, 0.195–0.3334) were found to be significant predictors of PU development. In both of these studies, the vaspressor agents included in the investigation were not defined, and analysis was limited to the dichotomous vaspressor variable of receiving vaspressors "yes or no." Kaitani et al18 operationalized vaspressors as the dichotomous variable catecholamine use — yes or no — yielding nonsignificant findings in a prospective cohort study of 98 ICU patients (type of ICU not specified). In this study, only two out of 11 (18.2%) patients who developed a PU received a vaspressor agent as compared to 14 out of 73 (16.2%) patients who received a vaspressor agent and were PU-free. Specific catecholamine agents included in this variable were not defined by the researchers. Emergent ICU admission and infrequent turning were reported as significant predictors of PU development in this sample of ICU patients.

By contrast, two studies found statistically significant associations between a generic vaspressor variable and PU development. In a retrospective study of 820 surgical ICU patients, Frankel et al18 found a significant relationship between the use of vaspressors and PU development only in univariate analysis. In this study, a statistically significant higher percentage of patients that developed PUs during the ICU admission received vaspressor infusions as compared to patients that remained PU-free (28% versus 11.8%, respectively, P = 0.02). No further description of the vaspressors included in this investigation was provided by the authors. Variables found to be significant in mul-

Table 2

<table>
<thead>
<tr>
<th>Feature</th>
<th>Vascular Endothelial Dysfunction</th>
<th>Sepsis/Septic Shock</th>
<th>Cardiogenic Shock</th>
<th>Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaspressors</td>
<td>Norepinephrine</td>
<td>Epinephrine</td>
<td>Phenylephrine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Vaspressors</td>
<td>Alpha (α)</td>
<td>Beta 1 (β1)</td>
<td>Beta 2 (β2)</td>
<td></td>
</tr>
<tr>
<td>Vaspressors</td>
<td>Cardiovascular</td>
<td>Hemodynamic</td>
<td>Immune</td>
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</table>
Multivariate analysis in this study included a history of diabetes mellitus (OR = 2.7, P = 0.023; 95% CI, 1.1–6.4), age >60 years old (OR = 3.7, P = 0.022; 95% CI, 1.2–7.1) creatinine >3 mg/dl (OR = 3.7, P = 0.019; 95% CI, 1.2–9.2), and spinal cord injury (OR = 16.8, P = 0.021; 95% CI, 1.5–182). Similarly, in a retrospective analysis of risk characteristics associated with PU healing in 87 patients with hospital-acquired PUs, Alderdeen et al13 found vasopressor infusion was associated with a five-fold increase in a nonhealing PU at discharge from the hospital (OR = 4.7; P = 0.005). This compared to patients with healed PUs at discharge. In addition, a comorbid diagnosis of spinal cord injury (OR = 1.5, P = 0.02) and age ≥40 years (OR = 7.02, P = 0.001) were significant associated with nonhealing PUs. In Alderdeen et al’s study,31 32 of the 87 patients with hospital-acquired PUs received vasopressor infusions during the ICU admission, and of these 23 (72%) experienced a nonhealing PU. No definition was provided by the authors regarding the specific vasopressor agents included in the investigation.

In two studies, the vasopressor variables under investigation were clearly defined by the researchers, including the specific agents; however, in both studies, analyses were limited to one single amalgamated vasopressor variable. In a retrospective cohort study, Tschanne et al2 reviewed medical records of 3,225 patients who underwent a surgical procedure and were admitted into one of five ICU/intermediate care settings. Specific types of ICUs were not identified in this study. A conceptual description of vasopressor agents included dopamine, norepinephrine, phenylephrine, and vasopressin; however, in multivariate analysis, use of vasopressors was the dichotomous variable reported. In this study, patients who received vasopressors were 33% more likely to develop a PU (OR = 1.33; 95% CI 1.03–1.73; P = 0.03), as compared to patients that did not receive vasopressor agents. Of the 383 patients who developed a PU, 163 (43%) received a vasopressor agent during ICU admission. In addition, the following factors also were found to be significant predictors of PU development in multivariate analysis in this study sample: low body mass index (OR = 0.97, P < 0.001; 95% CI, 0.95–0.98), history of diabetes (OR = 1.49, P < 0.001; 95% CI, 1.14–1.95), number of surgeries (OR = 2.23, P < 0.001; 95% CI, 1.45–3.44), total operating room time (OR = 1.07, P < 0.001; 95% CI, 1.03–1.11), admission Braden Scale score (OR = 0.89, P < 0.001; 95% CI, 0.86–0.93) and risk of mortality score (Level 4 score: OR = 11.15, P < 0.001; 95% CI
epinephrine was the only vasopressor included in this study analysis. For analysis.

epinephrine, epinephrine, or high-dose dopamine (>5μg/ kg/ minute) during the ICU admission. The vasopressor variable was found to be significant in univariate analysis (P < 0.001) but not to be predictive of PU development in this ICU sample. Of the 121 patients who developed a PU, 90 (74.4%) received vasopressor therapy during their ICU admission. Other factors in this study found to be predictive of PU development included male gender and subjective skin descriptions that included moist skin, edematous skin, mottled skin, and reddened skin.

Two studies provided the specific vasopressor agents used in analyses. In a prospective cohort study of 286 ICU patients (type of ICU not specified), Theaker et al16 found norepinephrine to be a significant predictor of PU development in this study sample, in addition to the following variables: APACHE II scale score, fecal incontinence, anemia, and prolonged length of stay. Norepinephrine was defined as a dichotomous variable, operationalized as infusions ≥60% of the ICU stay or infusions of <40% of ICU stay. Patients who received norepinephrine for ≥60% of the ICU admission were eight times more likely to develop a PU compared to patients who received norepinephrine for shorter durations or received no norepinephrine during the ICU admission (OR = 8.11; 95% CI 3.64 –18.0; P < 0.001). Norepinephrine was the only vasopressor included in this study for analysis. In a retrospective analysis of PU predictors in 347 medical/surgical ICU patients, Cox15 defined vasopressor administration as the total number of infusion hours during the ICU admission of each of the following agents: norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin. In univariate analysis, only norepinephrine and vasopressin were found to be significantly associated with PU development in this sample; in multivariate analysis, norepinephrine was found to be a significant predictor of PU development in this ICU sample (OR = 1.017; 95% CI 1.001-1.033; P = 0.04).

The mean hours of norepinephrine infusions in patients with a PU Stage II or higher (Stage III, Stage IV, unstable, or sDTI) was significantly higher (55 hours) compared to patients who remained PU-free (4 hours) (t = -4.00; P ≤ 0.01). In this study, 32 of the 65 (49%) of patients that developed a PU received norepinephrine. Other PU risk factors found to be significant predictors of PU development in multivariate analysis in this study included age (OR = 1.033; P = 0.03; 95% CI, 1.003–1.064), longer ICU lengths of stay (OR = 1.008, P < 0.001; 95% CI, 1.004 –1.012), history of cardiovascular disease (OR = 3.380, P = 0.02; 95% CI, 1.223–9.347), the admission Braden mobility subscale score (OR = 0.439, P = 0.04; CI 95%, 0.210–0.95), and the admission Braden friction/shear subscale score (OR = 5.715, P = 0.01; 95% CI, 1.423–22.95).

Only one study was identified that considered the effect of dose of a vasopressor agent on PU development. In a prospective pilot study of 16 hyperglycemic, mechanically ventilated critical care patients admitted to a long-stay (>24 hours) perianesthesia care unit (PACU), Concepcion et al10 found that moderate-high dose norepinephrine (defined as ≥2.5 mg/hour) infusion was significantly associated with reduced peripheral tissue perfusion (ρ = -0.53; P = 0.017). The proportion of patients with a PU was significantly higher in patients receiving moderate-high dose norepinephrine than in the patients who received low-dose norepinephrine (< 2.5 mg/hour) (P = 0.038). Norepinephrine was the only vasopressor under investigation in this study.

Discussion

Considered collectively, the studies in this review provide an emerging body of empirical support for vasopressor agents as a risk factor for PU development in critical care patients. Four studies identified vasopressor agents as a significant predictor of PU development in critical care patients,11,16,31,32 and three studies demonstrated significant associations in univariate analyses.14,15,17,30 However, caution is advised when interpreting these results, because many gaps remain in the literature. Studies examining the effects of specific vasopressors, dosing considerations, and duration of vasopressor administration on PU development are scarce in the literature. Moreover, no studies examined the effects of the use of multiple concomitant vasopressors. Variability in the measurement of vasopressors across study analyses also clouds the ability to draw clinically meaningful conclusions from the findings in this review.

In most of these studies, vasopressor agents were identified as one collective variable; six out of the 10 studies dichotomized vasopressors agents for analysis as a “yes or no” variable.14,15,17,19,31,32 Five studies11,16,17,30,31 identified the specific vasopressor agents under investigation; however, only three of these studies11,16,30 utilized individual vasopressors as distinct variables for inclusion in analysis. In two of these studies,16,30 the investigation was limited to only norepinephrine.

In the three studies in which individual vasopressor agents were used in analysis, variation in the operationalization of the agents was evident across studies. Although Theaker et al16 dichotomized norepinephrine by the amount of time the drug was administered, (≥60% of the ICU stay or ≤40%), Cox15 investigated the total infusion times during the ICU admission for each of the vasopressor agents as continuous variables. In the Concepcion et al study,30 patients were dichotomized into two groups based on norepinephrine dose (≥2.5 mg/hour or <2.5 mg/hour), and analysis was based on the average daily dose of norepinephrine received. In all three of these studies, norepinephrine was found to be a significant predictor of PU development; however, in two of these studies,16,30 norepinephrine was the only agent included in the investigation. Therefore, while empirical support is increasing for the broad
category of vasopressors as a PU risk factor, only a small body of evidence is emerging to support the role of one specific vasopressor (norepinephrine) to PU development.

All vasopressor agents are not equal and are not used interchangeably in clinical practice. Although many agents exert similar effects on the body, their indications for use will differ based on the receptors targeted by the medication. For example, norepinephrine, a first-line agent in the treatment of septic shock, exerts beta-1 (β1) (increased cardiac contractility, elevated heart rate, elevated cardiac output) and alpha (α) activity (potent vasoconstriction), while epinephrine exerts potent beta-1 adrenergic activity and is used as a first-line treatment in management of anaphylaxis and hypotension postcardiac bypass grafting.22 Vasopressin, a second-line agent used in the treatment of septic shock, produces vasoconstriction through V1 receptors located in the vascular smooth muscle.33 As noted, these agents all differ in their physiologic effects as well as clinical indications — thus, the paucity of empirical evidence regarding the effect of individual vasopressors on PU development renders it difficult to discern which vasopressor agent has the potential to produce the greatest deleterious effect on the skin.

The clinical effect of vasopressors also can vary based on the dose administered. For example, dopamine administered at lower doses produces a vasodilatory effect in the renal, mesenteric, coronary, and cerebral beds, but at higher doses, dopamine exerts the opposite physiologic effect, eliciting vasoconstriction.22 Similarly, vasopressin administered at higher doses (>0.03 U/minutes) is associated with potent vasoconstriction; however, at lower doses vasopressin induces vasodilation of the cerebral, renal, coronary, and pulmonary beds.33,37 During shock states, vasopressors are titrated with the goal to maintain the MAP ≥65 mm Hg.35 Thus, the dose of the vasopressor agent is dependent on the patient’s MAP response to the medication. Escalating doses translate into increasing peripheral vasoconstriction. Excessive vasoconstriction decreases blood flow to the vital organs. With regard to PU development, hypoperfusion of the skin due to hypotension, shock states, or dehydration compromises blood flow to the skin, increasing ischemia, which can profoundly impact the perfusion of deep tissue structures and result in PU development.8,18 Dosing of vasopressors was only considered in one small pilot study of 16 patients,30 and this study evaluated only one agent (norepinephrine). In this study, the average daily dose of norepinephrine was studied in two groups (patients receiving doses of either greater or less than 2.5 mg/hour). However, the dosing described in this study is not representative of the usual dosing of this medication. Usual dosing of norepinephrine in the treatment of shock is reported at 8–12 mcg/minute or 0.01–3.0 mcg/kg/minute.19,41

In the current state of the evidence, the “tipping point” with regard to vasopressor dose and PU risk cannot be determined. Although higher doses of vasopressors are presumed to be significantly related to PU development, empirical evidence to support this proposition is lacking. Thus, it is impossible to guide bedside practitioners regarding the dosing thresholds that could potentially contribute to PUs.

In addition to dosing of a particular vasopressor agent, the effect of the duration of vasopressor infusion on PU development has been subject to limited investigation. In one study,16 patients who received norepinephrine for more than 60% of their ICU stay were eight times more likely to develop a PU; and in another study,11 longer infusion times of norepinephrine emerged as a significant predictor of PU development. Longer infusion times of vasopressin were also significantly associated with PU development in univariate analysis in this study.11 The limited amount of empirical evidence provides preliminary support for the relationship between longer infusion times of norepinephrine and PU development; however, it may not offer clinically relevant information to clinicians. It is unknown if any time threshold exists with regard to the duration of vasopressor infusions and PU risk. Additionally, the combined effects of individual vasopressor agents, dosage, and duration of administration have not been studied.

The physiologic effect of simultaneous administration of more than one vasopressor also must be considered. In septic shock, one of the most common diagnoses necessitating admission into a critical care unit, vasopressors are a first-line treatment administered after aggressive fluid resuscitation.35,37 Current Surviving Sepsis guidelines34,35,37 support the use of norepinephrine as a first-line agent with doses titrated up to 20 mcg/minute to maintain a MAP ≥ 65 mm Hg with the goal of improving end-organ perfusion. If the desired clinical response is not achieved, a second vasopressor, usually vasopressin, is added to the treatment protocol. The addition of vasopressin, a potent vasoconstrictor in its own right, can diminish the dosage requirements for norepinephrine.34 If hypotension remains refractory to these agents, a third vasopressor agent can be added,22 usually epinephrine.35,37 No known studies have investigated the effect of concomitant use of multiple vasopressor agents on PU development; therefore, it is unknown whether the use of multiple vasopressors poses a greater risk than use of a single agent. This is another area ripe for investigation.

It is purported that hypotension shunts blood flow away from the skin surface to more vital organs, thus diminishing tissue tolerance for pressure, leading to capillary closure at lower levels of interface pressure that can result in PU development.12,24 In critical illness, hypotension either in the presence of inadequate fluid volume or which is refractory to aggressive fluid resuscitation requires the use of vasopressor agents in order to improve tissue perfusion and end organ function. When a PU develops in a critically ill patient requiring vasopressor support, it may be difficult to discern if the hypotension necessitating the use of vasopressors or if the powerful vasoconstricting properties of these agents contributed to PU development. The evidence is not strong enough.
supporting hypotension as a risk factor in the population due to the fact there is more frequent monitoring and interventions initiated quickly (such as vasopressors) to elevate blood pressure. On the other hand, there is evidence to document ischemic skin changes that occur on the body (ie, fingers/toes) following vasopressor administration. However, in the limited number of critical care studies that investigated the role of hypotension in PU development, hypotension has not been found to be a significant predictor of PU development in this population.23 Based on these side effects, it is plausible to the fact that in ICU patients, blood pressure is continuously monitored, resulting in earlier implementation of interventions aimed at elevating blood pressure through the use of, among others, vasopressor agents. On the other hand, the deleterious effect of vasopressor administration on the skin has been documented. Potent vasoconstriction produces inadequate perfusion to the fingers and toes, as well as peripheral ischemia, especially in patients with known peripheral vascular disease.24 Based on these side effects, it is plausible the vasoconstricting properties also could be a contributing factor in PU formation.

Despite quality care and best practice, PUs develop in hospitalized patients, and for persons admitted to an ICU the risk is even greater.46-47 Critical care units provide technologically sophisticated care to the sickest patients in the healthcare system. In the initial days of the ICU admission, patient survival is the overriding goal, requiring all members of the critical care team to manage multiple life-saving technologies while simultaneously trying to prevent a PU. Even with consistent skin assessments and the implementation of evidenced-based PU prevention strategies, PU development in ICU patients may be unavoidable.47 It is not possible to terminate vasopressor administration in an effort to mitigate PU risk, because this treatment modality holds enormous life-saving potential. In these patients, the prevention of a PU may be found to be unavoidable. The paradox is that the occurrence of a PU in a hospitalized patient is considered a “never event,” leaving caregivers in the challenging situation of trying to prevent a PU that may not be preventable.

Implications for Research and Practice

The current state of the evidence regarding PU development and vasopressor agents provides only preliminary empirical support to translate into practice. Many unanswered questions remain to be investigated. Studies examining the effects of type, dose, and duration of vasopressor agents would provide clinically relevant information for bedside clinicians when evaluating a critically ill patient’s risk for PU development. It is unknown in the current level of evidence if higher doses of a particular vasopressor agent for a short period of time or if lower doses for an extended time period expose the patient to greater PU risk; thus, it is difficult for clinicians to determine at what point a patient’s level of PU risk escalates. Moreover, studies that examine the synergistic effects of multiple concomitantly administered vasopressor agents on PU development are absent but would be equally beneficial and could provide clinicians with evidence that could be translatable at the bedside.

Empirical investigation into the pharmacodynamic effects of vasopressors on the skin is another potential avenue worthy of exploration. Studies that examine the impact of these medications on the cellular and tissue level hold the potential to enhance knowledge regarding the etiology of the pathophysiologic changes that occur at the skin and deeper tissue layers with administration of these agents. Additionally, such investigations may provide evidence surrounding the occurrence of the unavoidable PU.

Due to the critical burden of illness experienced by ICU patients, essentially all are “at risk” or even at “high risk” for PU development. Therefore, the implementation of prevention strategies as outlined in the current PU clinical practice guidelines26,27 must be standard practice in the ICU setting in an effort to avert PU development. Hypervigilance to PU risk is essential and should include an awareness of factors not currently measured in formalized PU risk assessment scales in this population. Vasopressor administration may be a risk factor that necessitates stronger consideration in PU risk assessment in the ICU population. However, based on the current level of evidence, the ability to impede PU development in patients receiving these agents has not yet been fully elucidated.

In the United States, the Braden Scale for Predicting Pressure Sore Risk49 is the most widely used risk assessment tool across diverse patient care settings, including the critical care setting. Evidence supporting the Braden scale’s ability to predict PU development in the critical care population is limited,7,10,15,50,51 and the scale does not take into consideration unique factors that potentially confront this population, including the use of vasopressor agents. Additional study into formalized PU risk measurement in this population with consideration for the inclusion of vasopressor agents in a critical care-specific PU risk assessment scale is another area that warrants further investigation.

Empirical evidence is the basis of clinical practice. Without it, clinical practice can be ineffective, fragmented, and result in negative patient outcomes. Vasopressor agents are mainstream treatments in critical care, with ever-increasing bodies of evidence to support their use in improving survival rates for these undeniably sick patients. Understanding the specific role these agents may play in PU development is quintessential in improving patient quality of care. Enhancing the current level of evidence is the first step. Translating the evidence into tangible information that can be incorporated into everyday practice by frontline caregivers is the ultimate goal. If future studies confirm that use of these agents is an independent risk factor for
PU development, providing concrete evidence regarding the type, dose, and duration of various vasopressors in relation to PUs empowers caregivers to anticipate risk and act accordingly. Conversely, a greater understanding of the pathophysiologic changes that occur in the skin as a result of vasopressor administration can provide clarity in determining if PU occurrence is unavoidable in patients receiving these agents.

Conclusion
Vasopressor medications are first-line treatment modalities for hypotension; they prevent end-organ dysfunction in contemporaneous ICU patients. The current level of empirical evidence regarding the role of vasopressor agents in PU development in the critical care population is in its infancy. Although empirical support exists for vasopressors as a broad category, and a smaller emerging body of evidence supports the use of norepinephrine as a risk factor, little is known about the impact of individual agents, the dose and duration thresholds for these agents, or the combined effects of multiple vasopressor agents administered simultaneously on PU development. Developing an empirically sound, comprehensive understanding of the role vasopressors play in PU development in critical care patients can result in a more informed bedside clinician who can translate this evidence into everyday practice with the patient deemed the ultimate benefactor.

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References