**Knowledge Gaps in the Etiology and Pathophysiology of Incontinence-Associated Dermatitis: A Scoping Review**

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# Abstract

Incontinence-associated dermatitis (IAD) occurs due to the prolonged exposure of the skin to urinary, fecal, or double incontinence. It represents a major challenge for clinical practice and significant financial burden. The aim of this scoping review was to identify and critically appraise the results of published studies on the etiology and pathophysiology of IAD and highlight the current gaps in empirical evidence. The electronic databases PubMed, Cumulative Index to Nursing and Allied Health Literature, Medline and Embase were searched for relevant papers published from 1996 up to April 2018. Studies and review articles related to the etiology and pathophysiology of IAD were included. Results from the current scoping review showed that despite the increasing interest in IAD, mainly from a clinical perspective, research directly investigating the underlying mechanisms causing IAD remains sparse. This represents a clear gap in knowledge, where further research is required.

**Key words:** Etiology; dermatitis; incontinence; incontinence-associated dermatitis; moisture-associated skin damage; nursing; pathophysiology; skin integrity; systematic review

# Introduction

Incontinence-associated dermatitis (IAD) is caused by the prolonged exposure of the skin to urine, stool or both1. Clinical manifestations are erythema and edema of the skin surface and if left untreated can lead to swelling, blister formation and to a vicious cycle of inflammation and eventually skin breakdown. Secondary infections, mainly fungal infections, may also develop due to increased susceptibility of the skin to invasion by pathogens2. Incontinence associated dermatitis also causes significant pain and discomfort, which can ultimately lead to a loss of independence and reduced health related quality of life1,3,4.

## Prevalence and Incidence of IAD

Prevalence and incidence are two epidemiological terms that are often confused. Therefore, for clarification reasons, it should be mentioned here that prevalence refers to the proportion of a population (expressed as a percentage) that suffers from IAD at a given time, whilst incidence can be defined as the rate of new cases of people who develop IAD during a period of time (e.g. month, year)5. Prevalence rates for IAD vary considerably between different care settings and range between 5.2% to 50%2,6–11 while incidence rates range from 3.4% to 25%12–14. In a very recent multicenter retrospective study, the prevalence of IAD was examined using a retrospective analysis with logistic regression analysis of adult patients in acute care, long-term acute care, and rehabilitation facilities in the United States and Canada15. Prevalence of IAD was estimated among all patients surveyed, among the incontinent patients only, across multiple care settings, and by incontinence type. Data from patients were collected using the 2016 International Pressure Ulcer Prevalence sur­vey and were analyzed using logistic regression. The estimated prevalence of incontinence and IAD in the entire population were 4.3% and 18%, respectively. With respect to incontinent patients only, the figures were much higher, with the prevalence of IAD reported to be 8.4% in long-term care and 19% in acute care facilities15. In addition, a recent study7 collected data from 5342 adult patients in acute care facilities in 36 states in the United States7. Results demonstrated that the overall prevalence of IAD was 21.3% in the entire population, whereas among incontinent patients, who represented 46.6% (n=2492) of the population, the prevalence of IAD rose to 45.7%7. With respect to the prevalence of IAD in nursing homes, this was examined in a study by Boronat-Garrido and colleagues (2016)6 using the Incontinence-Associated Dermatitis Intervention Tool-D (IADIT-D)16,17. In this specific study, a secondary analysis of 3 consecutive cross-sectional multicenter studies was conducted, involving 5785 patients and 78 nursing homes in Germany from 2012 to 20146. The reported prevalence of incontinence (any type) was 68.3%. After the exclusion of patients without data, the prevalence of IAD was estimated among 3406 patients (58.8%) and was found to be 5.2%6. In another cross-sectional observational study conducted across nine tertiary hospitals, in China, all patients (n=13176) with length of stay of over 24 hours were recruited and a very low prevalence rate (0.73%) of IAD was reported . In particular, from the 97 IAD cases identified, more than half (64.95%) represented hospital-acquired cases, 25.77% cases at home and only 9.77% attributed to community hospital cases10. Furthermore, in another study conducted among 8365 patients in 66 acute and community hospitals in Wales, the reported prevalence of IAD was reported to be 4.3%11. In most of the studies, the prevalence of IAD was reported in relation to both the entire study population and incontinent patients allowing direct comparisons to be made. However, these figures may not be truly representative due to the previous lack of validated assessment tools, the confusion with superficial pressure injuries, and the lack of consensus in many countries on assessment criteria for the diagnosis of IAD18.

In this respect, several categorization tools have been developed for IAD assessment14,19–22, however these tools are not widely used in clinical settings since evidence is lacking whether they can actually inform clinical and patient care1. Recently, a panel of experts developed a simple IAD severity categorization tool (Ghent Global IAD Categorization Tool) for use in clinical and research settings.3,9 This instrument comprises three categories for assessing IAD.1,9. Recent work, involving an international sample of 823 health professionals, showed increased sensitivity of the GLOBIAD in diagnosing between intact but erythematous skin and skin loss. However, clinical signs of infection were difficult to be determined, as these cannot be assessed merely by photographs. Indeed, this work is a step forward towards the development of an internationally accepted IAD categorization tool, however, further work is required.21

## Prevention and management of IAD

Prevention and management strategies of IAD are costly for both hospital and community settings. The primary preventive measure against the development of IAD is to minimize the exposure of skin to incontinence. Current best evidence suggests a preventive intervention must include four main strategies: 1.) structured skin care regimen to cleanse the skin and protect from additional exposure to urine or fecal matter, 2.) use of products that absorb moisture from the skin, 3.) removal of the source of excessive moisture and, 4.) treatment of any secondary cutaneous infections.23. Additionally, a recent scoping review suggested that barrier creams, liquid polymers and cyanoacrylates can be used to protect skin barrier function by maintain its hydration levels but also to block the entry of harmful substances24.

Skin care regimens typically include the use of soap and water to cleanse the area at risk, followed by the use of a moisturizer and/or a skin protectant5. However, a seminal study reported that frequent cleansing with soap and water, and drying using a towel damages the skin barrier, reflected by an increase in transepidermal water loss (TEWL) and skin pH 25.

## Problems in IAD research

In spite of the increasing interest in IAD, an exact definition of this condition is not listed in the World Health Organization’s International Classification of Diseases (ICD-10)26. Instead, it contains a detailed description of diaper dermatitis which is sometimes confused with IAD27. This constitutes a major problem in clinical practice as diaper dermatitis occurs in infants and should be distinguished from IAD that occurs in adults and particularly in the geriatric population 28. Labelling IAD as diaper dermatitis is problematic due to: 1) significant differences in skin barrier function, and 2) differences in skin area.5,29–31 Additionally, there is a lack of consensus on the terminology of IAD, as other terms such as irritant dermatitis, perineal dermatitis and moisture lesions are also used to describe IAD. As a consequence, progress in IAD-related research is hampered 1. Therefore, the aim of this scoping review was to identify and summarize published literature, including original research articles and reviews, on the etiology and pathophysiology of IAD to uncover gaps in current knowledge, and provide directions for future research.

# Methods

The current review was conducted using systematic search and filter procedures and was based on the methodological framework for scoping reviews developed by Arksey and O'Malley32. The electronic databases of PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, and Embase via OvidSP were searched for published papers from 1996 to April 2018 to identify relevant published literature. The earliest search year for the current scoping review was set to 1996 as it is the year when the first pathophysiological framework of ‘‘perineal dermatitis’’ was developed33 that tried to capture the multifactorial nature of this condition, and was also adopted by recent frameworks34. All combinations of search terms (Table 1) used the Boolean operators ‘‘OR’’ and ‘‘AND’’. The inclusion criteria were as follows: 1) original studies and review articles, 2) published in English due to the high translation costs, and 3) related to the etiology and pathophysiology of IAD. On the contrary, exclusion criteria included: duplicate publications, articles without the full text available and studies related to the prevention and management of IAD.

## Outcomes

The initial search retrieved 1408 records: 70 in PubMed, 580 in CINAHL, 710 in Medline, and 48 in Embase via OvidSP (Figure 1). Articles without the full text available were excluded, reducing the number of articles to 1041. Filtering for articles published in English reduce the number to 1031. After screening of titles and abstracts, studies related to prevention and management of IAD were excluded, and 135 eligible articles were identified. After duplicate removal, 13 studies and review articles were included in this scoping review, including their reference lists. Table 2 provides a summary of the studies and review articles included in the current scoping review.

## Theoretical models of IAD pathophysiology

Theoretical models of diaper dermatitis have been adapted to describe and explain the pathophysiology of IAD. The first conceptual model on diaper dermatitis shows limited understanding of the clinical problem as only tissue tolerance, type of incontinence and toileting ability are identified as risk factors for IAD35. A few years later, the role of skin pH was highlighted, and specifically its shift to alkaline levels by the action of fecal enzymes and ammonia. Additionally, the authors suggested that frequent cleansing regimens lead to physical and chemical irritation of the skin. IAD was also identified as a risk factor for the development of pressure injuries due to increased susceptibility of the skin to shear33.

More recent models highlight the multifactorial nature of IAD5,31,34. The model developed by Gray and colleagues, which is based on previous studies 36,37, gives a detailed explanation of the physiological response of the skin to incontinence. It is proposed that following exposure there is an increase in TEWL, an indicator of reduced skin barrier integrity 38, and pH, leading to a vicious circle of increased inflammation, evidenced by cytokine and histamine release. In agreement with Jeter and Lutz33, Beeckman and colleagues34 also proposed that IAD development is dependent on the frequency of cleansing regimens. It was also suggested that cleansing activities lead to an increased permeability of the skin and to an impaired barrier function. Bacterial colonization and secondary infections also have been proposed as contributing factors to IAD34. Unfortunately, these models are based on clinical experience rather than direct empirical data.

## Etiologic Factors

Incontinence represents the main etiologic factor for the development of IAD. However, it should be acknowledged that IAD has a complex multifactorial pathophysiology where other factors and secondary infections are involved5,34. As identified in the literature contributing factors involved in IAD development include: 1) the chemical content of the moisture source, 2) frequent cleansing, 3) duration and frequency of exposure, 4) the inflammatory response triggered in the skin and 5) secondary infections.

### Moisture source

As the name implies, incontinence (urinary, fecal or double) is the main risk factor for IAD. Therefore, we hypothesize that the severity of the skin damage depends on the moisture source and its chemical constituents. Urine is mainly composed of water (95%), urea, and several organic/inorganic compounds. However, its composition varies between individuals, as it is influenced by many factors such as ethnicity, diet, environmental conditions, time of the day and excretion of drug metabolites 39. Biological urine has a pH ranging between pH 4.8-8.0 40–43.

The mechanisms underlying skin barrier disruption following urine exposure are not entirely understood23, but it has been proposed that over-hydration of the epidermis, swelling of corneocytes and maceration of the skin contribute to skin damage.44 In particular, in the study conducted by Warner and colleagues (2003)45 forearm skin was exposed to water and urine for prolonged periods (4h and 24hrs), and histological analysis revealed extensive disruption of the intercellular lipids of the stratum corneum, induction of large pools of water not only in the intercellular space but also in the corneocytes resulting in pooling of water in intercellular space, as well as trapping of solutes in corneocytes which create an osmotic pull, increasing damage that occurs with frequent exposure45. Skin damage is aggravated in the presence of fecal bacteria that convert urea in urine into ammonia by the reaction of urease enzyme46, thus shifting the pH to alkali levels and away from the protective acid mantle of the skin surface. This alkaline environment is associated with a disrupted skin barrier function, as key lipid-processing enzymes, including β-glucocerebrosidase, which are critical for barrier synthesis, are active in an acidic environment47. Studies related to diaper dermatitis have showed that diapers produce a significant increase in TEWL and pH, compared to undiapered skin, and these were associated with the severity of diaper dermatitis 29,48. However, these studies were performed in infants and any direct comparison with IAD should be avoided, although they do offer some insight into the problems caused by occlusion of the skin and the use of absorbent products in the management of incontinence.

With respect to IAD, a few studies attempted to investigate the role of urine. In one study, infant urine was applied for three days on adult skin on three anatomical sites, two on the arm and one on the back49. Urine was applied on normal skin sites and on sites where the skin barrier was compromised by tape stripping, excessive hydration or both. As negative and positive controls, saline and sodium lauryl sulphate (SLS) were used respectively. Results showed that urine produced a higher degree of erythema compared to saline, but less than that caused from the SLS treatment. On the contrary, urine led to a significant increase (p<0.05) in skin pH compared to both control and SLS, and this was not dependent on the condition of the skin49. Skin barrier function was not assessed in this study. The use of infant biological material on adult skin, clearly limits the physiological and clinical relevance of findings, due to differences in urine composition between infants and adults42,50. Due to the similar response between infants and adults, the authors claimed that both can be used in diaper dermatitis or IAD research. This assertion is also limited due to differences in skin characteristics and susceptibility to irritants in infants and adults.

In another recent study, an experimental model of IAD was developed using synthetic-urine (s-urine) and ammonium hydroxide (% w/v), to adjust its pH to alkali levels (between pH 7.9-10.7)51. In the preliminary investigation, human volunteers (n=6) had their forearms exposed to different s-urine solutions for six hours. An erythematous skin response was observed as determined by both a visual scoring system and the changes in blood flow. In addition, the degree of erythema and the severity of skin barrier disruption were associated with increasing concentrations of ammonium hydroxide and accordingly pH. On the contrary, there was no significant effect on skin surface pH. Subsequently, the forearms of volunteers were exposed to an alkaline s-urine solution (pH=10.3) for six hours daily for a period of five days, and a visible erythema and a significant increase (p<0.05) in blood flow were observed compared to saline control sites. There was also an increase in TEWL compared to baseline values, obtained on the day prior application, but was only significant (p<0.05) after the fourth day of exposure. Again, there were no significant effects on skin pH.

In spite of these informative results, we assert that this model is not representative of the physiological and clinical conditions that lead to the development of IAD. Our rationale for this conclusion is based on the following observations: 1.) the urinary pH values used were beyond the levels of biological urine, 2.) the exposure time (6 hours) is longer than the frequency at which incontinent patients are checked for wetness in clinical practice, and which is normally two hours 25, 3.) the effects of wetness, water per se, and occlusion were not considered and distinguished from the effects of s-urine, and 4.) exposure was limited to synthetic urine. In view of these limitations the exact relationship of urine and its inherent pH on IAD development needs to be elaborated in future studies.

In a recent study the features that lead to the development of IAD in clinical facilities were more closely simulated in an experimental setting52. In particular, 30 female participants (>65 years) had their hip and buttocks regions exposed to an incontinence pad soaked with 400ml s-urine (pH 8.0)53 for 4 hours during which they laid in a supine position. Skin physiology and the integrity of skin barrier function were investigated using bioengineering methods, including TEWL, surface pH and skin hydration measurements, taken at baseline and at regular intervals (15 and 30mins, 1, 2 and 4 hours). Visual assessment of erythema was also performed. Results demonstrated that skin hydration and surface pH increased significantly after just 15 minutes of exposure compared to baseline values. Additionally, TEWL values increased significantly at the end of exposure period compared to baseline values52. In comparison with the study by Larner and colleagues (2015)51, although the exposure time to s-urine was lower (4hours) surface pH increased significantly. This can be explained by the larger skin area exposed to s-urine and the inherent buffering capacity of the skin54. More specifically, the elderly participants in the study by Phipps, Gray and Call (2019) were characterized with a diminished buffering capacity, as the buffering capacity depends on the thickness of the stratum corneum55 and is well-established that aging skin is characterized by decreased stratum corneum thickness56. On the contrary, the young cohort used in the study by Larner and colleagues (2015) had an intact buffering capacity of the skin that tightly controls pH, and any changes are only short-lived54.

##### Ammonia

The production of ammonia by fecal bacteria was first demonstrated several years ago, as a study shown that *Brevibacterium ammoniagenes* produces ammonia from urea, and when applied on the skin it causes an erythema57. This was also supported by another study, in which application of urine, smelling strongly of ammonia, for four hours on the buttock skin of infants produced an erythematous response58. Hence, ammonia was considered to be involved in the development of diaper dermatitis and subsequently adapted in models of IAD. However, years later, the role of ammonia on diaper dermatitis was challenged in a study by Leyden and colleagues (1977), who reported that ammonia concentration was higher in infants with no diaper dermatitis (n=63) compared with infants suffering from the condition (n=18), although the numbers of infants recruited were not equal. Subsequently, they showed that when infant buttock skin was challenged (24 hours) with adult urine (pH 8.0), treated with urease to produce ammonia, no erythema was observed. This was further demonstrated on adult forearm skin which was exposed to the same urine solution but with ammonium hydroxide added at various concentrations, but with the pH value adjusted to 8.0 using hydrochloric acid. Results showed that mild erythema is only evident after prolonged exposure to urine. Afterwards, the authors examined the effects of urine with low and high concentrations of ammonia, produced by urease, on adult skin that experienced skin barrier disruption by a scarification technique. Results showed an increased erythema on damaged skin following urine exposure compared to the saline control site, suggesting a secondary role of ammonia in the development of diaper dermatitis59. The main limitation of the study is that urine samples were filtered before application and this might have influenced the results. Although this study was related to diaper dermatitis, it produced interesting findings that need to be further explored in respect to IAD.

#### Fecal Materials

Formed stool is composed of about 75% water, protein, undigested fats and food residues, polysaccharides and bacteria. As with urine, its composition varies depending on diet including fiber and protein intake, and moisture content 60–63. The pH range of stool varies from a pH of 5.0 to 8.0 64. Clinical experience suggests that liquid stool is more damaging than formed stool, due to its higher composition of lipolytic (lipid-digesting) and proteolytic (protein-digesting) enzymes and alkaline pH, compared to solid formed stool that has a neutral pH and less metabolically active enzymes1,65. In addition, several studies have demonstrated that fecal enzymes are highly active in an alkaline environment29,66,67. In the study by Andersen and colleagues (1994)66, the back of healthy volunteers (n=11) was exposed to four different combinations of enzymes and bile salts solutions, prepared in buffers of pH 6.5 and 8.0. As positive and negative controls, SLS and phosphate buffer (pH 8.0) were used respectively, together with an untreated site. Solutions were applied for 21 days and measurements of TEWL and skin pH, and visible assessment of erythema were taken at days 5, 12 and 19 of exposure, at which treatments were removed and re-applied. Results showed that after the fifth day of exposure, all enzyme solutions and the SLS caused a visible erythema that was increasing until day 19, with the latter also producing the highest degree of irritation. With respect to the enzyme preparations, the one that was composed of high amounts of digestive enzymes presented to be the most irritant, as determined by the increase in TEWL and visible erythema. The enzyme solution containing lipase and trypsin (pH 8.0) was also very irritating but not evident until day 12. By contrast, the solutions containing elastase, chymotrypsin and trypsin, were less irritating but their activity was pH-dependent and increased in an alkaline buffer solution (pH 8.0) leading to a shift in skin pH to alkali levels (pH>7). However, the authors acknowledged that this might be attributed to skin barrier disruption from the alkaline buffer68. The main conclusion from the study is that when enzymes were prepared at pH 8.0 they showed increased irritancy, whereas buffer alone at a similar pH only showed mild or no reaction66. The main limitation of the study is that the enzymes and bile salts used corresponded to the concentrations in infant stool whereas subjects were adults, and this does not reflect the clinical reality of IAD.

In another study, the effect of fecal material was investigated on the barrier function of skin in both infants and adults. Fecal material was obtained from infants (n=16) by their mothers, who also participated in the study, and applied for 4 hours on two skin sites on the buttocks of infants and on two skin sites on the forearm of adults. An extra two sites on each anatomical site were also left untreated. Results showed that exposure to fecal material produced erythema in both infants and adults compared to the untreated sites, along with a significant increase in TEWL and skin pH (p<0.05). Subsequently, exposed sites were compromised by tape stripping (n=10) that led to a further increase in erythema based on visual assessment; though no significant changes in TEWL and skin pH were detected, suggesting that exposure to tool increases the susceptibility of the skin to other irritants. In spite of these results, the source of fecal materials was taken from infants with the limitations noted previously. Additionally, the fecal composition varies between infants and adults, including moisture content.62 Another limitation of that study is that each infant/mother was treated with the child’s own biological material and hence each subject received a different treatment.49

A more recent animal study also examined the biological effects triggered in the skin following exposure to pancreatin, an enzyme found in stool. Guinea pigs were exposed to 1%, 5% and 10% pancreatin solutions (pH=9.0) for 1, 3 and 5 days. Results showed that the severity of skin damage, assessed using a visual scoring system, was associated with pancreatin concentration and length of exposure. The maximum skin response was observed after 3 days of exposure and not after 5 days of exposure 69. Transepidermal water loss measurements were not taken to assess the skin barrier function, representing the main limitation of the study. The authors aimed at developing an animal model of IAD; however, the inclusion of just pancreatin clearly limits the generalizability of study findings.

Stool also contains intestinal bacteria that may create or exacerbate skin damage. The relationship between intestinal bacterial species and skin damage was demonstrated in a study by Mugita and colleagues (2015)70 that used Sprague-Dawley rats which had their dorsal skin exposed for 4 hours to a model of fecal-incontinence (agarose gel with various proteolytic enzymes: trypsin and chymotrypsin corresponding to physiological adult concentrations), followed by inoculation with a *Pseudomonas aeruginosa,* a common bacterium found in patients with incontinence71, for 30 minutes. Additionally, the contralateral side of the skin received no treatment (untreated skin) and was also inoculated with bacteria. Results showed an increased visible erythema on the proteolytic-treated skin but not on the untreated skin. Immunohistochemical analysis revealed the invasion of bacteria and the presence of inflammatory cells, including epidermal Langerhans cells and macrophages, in the deeper areas of the dermis. Accordingly, the authors concluded that the tissue damage in IAD is distinct from irritant contact dermatitis (ICD) which is restricted to the dermal-epidermal junction.70

Animal models are widely used in research; however, the physiological relevance of findings is limited due to differences between animal and human skin. With methodological developments there is an urgent need for *in vivo* studies in humans to investigate the pathophysiology of IAD.

#### Dual (Urinary and Fecal) Incontinence

In double incontinence (urinary and fecal), the severity of the skin damage increases compared to that caused by urine or stool alone. Indeed, a previous study showed that after prolonged exposure of hairless mice to a combination of urine and feces a high degree of erythema was evident46 indicating an inflammatory response.

### Frequent Cleansing

In clinical practice, multiple skin cleansing activities are required in response to frequent episodes of incontinence in order to cleanse the skin from the irritating urine and fecal material and promote patient comfort. However, frequent cleansing may on its own be damaging to the skin25, especially when frequent episodes of incontinence occur. This is supported by the study by Voegeli (2008)25, in which 6 standard washing and drying techniques were performed twice (every two hours) on the volar aspect of the forearm of participants (n=15). Skin integrity was evaluated using TEWL and skin pH measurements and results showed that repeated cleansing of the skin, with soap and water, leads to a significant increase in TEWL and skin pH, thus compromising the integrity of the skin25. In addition, Beeckman and colleagues34 proposed that frequent cleansing leads to increased skin permeability; however, there is no solid evidence to support this hypothesis. In a similar manner, physical irritation, such as friction, towel drying, and shear from clothing and incontinence pads, is also considered a contributing factor to IAD1,34,72.

### Duration and Frequency of exposure

Duration and frequency of exposure are critical in IAD with regards to the time to onset of IAD. In a study by Long and colleagues (2011)12, a cohort of 171 patients were examined in a long-term acute care setting and the reported incidence rate of IAD was 7.6% and the median time to develop was 13.5 (3-25) days12. In another secondary analysis study8 of a multicenter study73, involving over 900 nursing home residents and 16 nursing homes, the median onset of IAD was 13 (6-42) days8. With regards, to intensive care units, a study conducted in a surgical/trauma critical care unit involving 45 patients, mainly males, with fecal-incontinence the reported median time to IAD development was 4 (1-6) days in intensive care settings74.

In experimental settings, studies exposed the skin to urine and/or feces for various timings, ranging between 6 hours to 21 days46,49,51,53,66. However, the research results are not in agreement and this discrepancy may be attributed to the different pH values of the solutions. In particular, in the study by Mayrovitz and Sims (2001)53, the forearm skin of healthy volunteers was exposed to an s-urine formulation of pH 7.9 for 5.5 hours and results showed a decrease in blood flow53. On the contrary, a more recent study51 that used the same s-urine formulation but adjusting its pH to 10.0-10.9 with ammonium hydroxide demonstrated that exposure of forearm skin for up to 6 hours is adequate to cause a visible erythema51, This implies that the duration of exposure is pH-dependent. On the contrary, several studies reported that exposure to urine/feces for several days leads to a visible erythema and to the disruption of the skin barrier46,49,51,66. Nevertheless, the use of different skin models, the source of urine or fecal matter, and the various anatomical sites tested in those studies limit the extrapolation of the findings to IAD occurring in a clinical setting.

### Other factors

Incontinence associated dermatitis is multifactorial condition as moisture alone cannot cause skin breakdown.2,43,54-56 Other contributing factors include: 1) occlusion from absorbent products, 2) mechanical damage, and 3) infection from pathogens.2,75,76 With respect to occlusion, the damaging effects of urine and/or feces may be aggravated under occlusive conditions created by absorbent products used to contain urine or stool.9,75 However, a more recent study suggested that occlusion does not have a significant effect on healthy skin, and in fact it makes the skin less susceptible to irritation 68,77. Results are conflicting, but the effects of occlusion in research studies need to be determined and distinguished from the effects of urine versus fecal matter. Additionally, secondary fungal and bacterial infections can contribute to the development of IAD. As discussed in an earlier section, the conversion of urea to ammonia creates an alkaline pH environment which hinders normal skin microbiota and as a consequence promotes the growth of pathogenic bacteria, including *Staphylococcus aureus*78. The production of nitric oxide, which represents another protective mechanism against the growth of pathogens is optimum in acidic conditions79, and accordingly any changes in pH will favor the growth of microorganisms. Secondary opportunistic fungal infections (e.g. Candidiasis), are also very common and indeed it has been reported that 18% of IAD patients suffered from cutaneous candidiasis9.

### Inflammatory response of the skin in IAD

Incontinence associated dermatitis is an inflammatory skin condition. This was demonstrated in a clinical study, in which skin biopsies taken from patients with IAD were histologically examined and an inflammatory pattern was identified, characterized by partial loss of epidermis, dilated vessels with some swelling of the endothelium, edema of the dermis and presence of inflammatory cells.80 However, the inflammatory biomarkers associated with IAD development have not been identified yet, and we uncovered only one animal study which investigated the release of cytokines. In that study, the inflammatory mediators released following exposure to various concentrations of a fecal enzyme (pancreatin) at varying exposure times were examined. Results showed a significant dose-dependent increase in the levels of interleukin-2 (IL-2) and interferon-γ (IFN-γ)69. There are currently no human studies concerning the inflammatory response triggered in IAD and this represents a significant gap in current knowledge.

# Conclusions

Informative results were obtained from the current scoping review. With regards to IAD development, theoretical frameworks have been developed to describe its etiology and pathophysiology, but these are mainly based on clinical experience, animal studies and on studies in infants with diaper dermatitis. Indeed, there is a lack of strong empirical evidence to support the pathophysiology of IAD and there are knowledge gaps that still need to be filled. In addition, there is a necessity for research studies involving human participants. Accordingly, future studies should aim at elucidating: 1) the role of urine and its inherent pH on skin integrity, 2) the permeability and susceptibility of the skin to moisture following frequent cleansing activities and 3) the inflammatory response triggered following exposure to urine and fecal matter.

# Key Points

* The underlying pathophysiological mechanisms of IAD have not been fully elucidated yet
* *In vivo* studies with humans are required to investigate the pathophysiological events in IAD.
* Future studies should investigate: a) the role of urine and its inherent pH on skin integrity, b) the permeability and susceptibility of the skin to moisture following frequent cleansing activities and c) the inflammatory response triggered following exposure to urine and faeces.

**Table 1.** The search terms used in this systematic review of the literature using PubMed, CINAHL, Medline and Embase via OvidSP.

**Table 2.** Summary of the studies included in this scoping review

**Figure 1.** Flow chart showing the results from the systematic search of the literature.

**Table 1.** The search terms used in this systematic review of the literature using PubMed, CINAHL, Medline and Embase via OvidSP.

|  |
| --- |
| Search Terms |
| Incontinence-associated dermatitis OR incontinence associated dermatitis | **AND**  | etiology |
| pathophysiology |
| pathology |
| mechanisms |
| inflammation |

**Table 2.** Summary of the studies included in this scoping review

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Type of study** | **Aim of the study** | **Subjects** | **Conclusion of study** |
| Beeckman et al., 2009 | Literature review | To provide the current evidence on the prevention and treatment strategies for IAD |  | An appropriate skin cleansing and skin protection regimen is needed for IAD prevention |
| Beeckman et al., 2014 | Systematic-review and meta-analysis | To identify the association between IAD and pressure ulcers |  | There is a possible association between IAD, its most important etiological factors, and the development of pressure ulcers |
| Beeckman et al., 2018 | Development and validation study  | To design and psychometrically evaluate the GLOBIAD categorization tool | 34 experts from 13 countries | GLOBIAD instrument was developed but further work is required for its validation  |
| Beeckman, 2017 | Integrative review | To provide an update on IAD terminology, etiology, epidemiology, observation, prevention,and treatment |  | Skin maceration, chemical irritation, and physical irritation are important etiological factors for IAD |
| Black et al., 2011 | Review  | To review current knowledge on IAD and intertriginous dermatitis  |  | An optimal skin care is required for the prevention of IAD |
| Gray et al., 2007 | Review | To provide existing knowledge on IAD pathophysiology |  | Scientific evidence is lacking on IAD epidemiology, etiology, and pathophysiology. Future research is needed to identify novel interventions for IAD |
| Gray et al., 2011 | Review  | To review current knowledge on IAD pathophysiology  |  | Conditions defined as moisture-associated skin damage, including IAD, have common etiologies |
| Gray et al., 2012 | Review | To review current knowledge and research gaps on IAD pathophysiology  |  | There is a significant gap in knowledge on IAD epidemiology, etiology and pathophysiology |
| Ichikawa et al., 2014 | Cross-sectional comparative study | To reveal the physiological and appearance characteristicsof skin maceration associated with urine and/orfecal incontinence | Elderly women with urinary- and/or fecal- incontinence (n=63) | Erythema index is appropriate for identifying skin maceration caused by incontinence |
| Larner et al., 2015 | Experimental human study | To develop a cumulative human model of IAD | Healthy adults (n=6) | Exposure of the skin to alkaline (pH 10.3) s-urine for 6hrs per day over a five-day period produces a human model of IAD  |
| Mugita et al., 2015 | Experimental animal study | To determine the histopathological changes in the skin when exposed to proteolytic enzymes and bacteria  | Sprague Dawley rats (n=17) | Bacteria can penetrate macerated rat skin, and in combination with the digestive enzymes produce inner tissue damage and inflammation |
| Phipps, Gray and Call, 2019 | Experimental human study | To evaluate the effects of urinary incontinence on skin barrier function and assess the risk of IAD | Elderly women over 65 years old (n=30) | Exposure for 15 minutes to an incontinence pad containing s-urine led to a significant increase in moisture content and cutaneous pH (p<0.01). TEWL was also increased after 4 hours of exposure (p<0.01) |
| Voegeli, 2016 | Review  | To provide current knowledge on IAD and the challenges for clinical practice  |  | It is difficult to deliver evidence-based nursing care for IAD patients due to the lack of terminology and the numerous commercial products  |
| Warner, Stone, and Boissy., 2003 | Experimental human study  | To examine the effects of water and urine on stratum corneum integrity  | Healthy male adults (n=2) | Exposure for prolonged periods to water and urine leads to altered stratum corneum morphology, swollen corneocytes, disorganization of lipids and appearance of large pools of water |
| Wen et al., 2017 | Experimental animal study | To determine the biological changes in animal model following exposure to pancreatin | Male Guinea pigs (n=78) | The severity of skin damage was associated with increasing pancreatin concentration. a significant dose-dependent increase in the levels of IL-2 and IFN-γ was also observed |
| Woo et al., 2017 | Scoping review  | To summarize existing evidence on the managementand prevention of moisture-associated skin damage |  | Moisture can lead to severe skin damage, and the authors concluded that barrier ointments, liquid polymers, and cyanoacrylates can be used to protect skin barrier function against the harmful effects of moisture |



**Figure 1.** Flow chart showing the results from the systematic search of the literature.

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