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Cellulitis in chronic oedema

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Linked Article: Burian *et al.* Br J Dermatol 2021; **185**:110–118.

Cellulitis (also known as erysipelas) is a common infection of the skin and subcutaneous tissues, and therefore falls within the domain of dermatologists. Cellulitis, which can often be recurrent, is among the top 10 reasons for admission to hospital, with patients receiving treatment from many specialties including emergency care, general practitioners, general medicine, surgery, tissue viability and dermatology.[1]

In this issue of the *BJD*, Burian *et al.*[2] examine the prevalence of cellulitis in patients with chronic oedema. Chronic oedema is an easily identified clinical sign and leads to the same pathophysiological effects and appearances as lymphoedema, which is not so easily distinguished. Tissue fluid is predominantly drained by the lymphatic system and not by venous reabsorption as was previously thought.[3] This means that all chronic oedema, i.e. subcutaneous oedema persisting for at least 3 months, is caused either by an absolute reduction in lymph transport, as in lymphoedema, or by lymph drainage being overwhelmed by a fluid (lymph) load, such as that which occurs with higher venous pressures from heart failure or venous disease. Therefore, chronic oedema always represents lymph drainage failure, and as it is easy to identify and has the same physiological effects, it can be considered a surrogate for lymphoedema.[4] As lymph carries antigen related to infection as well as lymphocytes for an appropriate immune response, disturbed lymph drainage, whether owing to fluid load or lymph vessel dysfunction, results in immunodeficiency as a consequence of the disturbed immune cell trafficking.[5]

The novel findings from this publication are that one-third of patients with chronic oedema are likely to develop cellulitis at some point. The worse the oedema, the more likely cellulitis is to occur; the better the oedema, the less likely cellulitis is to occur. The strengths of this publication are the large number of patients included for study and the international collaboration involving nine countries, indicating that chronic oedema predisposing to cellulitis is a global healthcare burden – at least in these countries. By targeting healthcare professionals with an interest in lymphoedema to identify patients, numbers may have been falsely elevated and more severe cases included compared with the population at large, but this does not undermine the value of the results. Unfortunately, data on recurrent cellulitis were not included and this is likely to be a common occurrence. As shown previously, cellulitis can be self-perpetuating with past episodes making future episodes more likely.[6] While prophylactic penicillin has been shown to be of value in preventing cellulitis,[6] this study demonstrates the importance of controlling the chronic oedema in preventing cellulitis, a finding recently confirmed by the use of compression garments to prevent cellulitis.[7] So often in healthcare, patients are treated for the acute episode of cellulitis and discharged without sufficient consideration being given to treatment of the risk factors, such as chronic oedema, skin disease and wounds. Dermatologists are well placed to manage such conditions and therefore should be more involved in cellulitis care. The Norwich model has shown the value of dermatological input for cellulitis,[8] particularly as red legs do not always mean cellulitis and mismanagement frequently occurs.[9]

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Using epidemiological methods to quantify the risk of serious infections in children with atopic dermatitis

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In their article in this issue, Droitcourt *et al.* investigate the risk of some systemic infections leading to hospitalization in children with atopic dermatitis (AD) compared with sex- and age-matched comparators in Denmark.[1] Studied outcomes were upper and lower respiratory tract, gastrointestinal tract, musculoskeletal tract, urinary tract, heart and central nervous system infections and sepsis. Infections treated in hospitals were regarded as serious infections, and AD was defined as at least one recorded diagnosis of AD, but an algorithm may have captured more children with AD.[2]

The authors performed a cohort study using the nationwide Danish population and health registers applying survival analysis,[3] comparing time from study inclusion to first infection between children with AD and comparators. The authors conclude that children with AD have an increased risk of systemic infections requiring hospitalization. This work is of importance to patients and physicians to raise awareness of a possible increased risk of serious infections.

The authors studied incident infections, however, there is no information on exclusion of those with prior infections, and recurrent infections would reflect the real world to a larger extent.[4] The authors maybe censored children at the first infection during follow-up, which makes sense statistically. On the other hand, children with many prior infections might be at higher risk for a new infection.

The adjusted and the fully adjusted model for lower respiratory infections yields nonoverlapping confidence intervals, which is unusual. Maybe asthma/hay fever is an intermediator on the pathway between AD and lower respiratory infection rather than a confounder.[5] From the baseline table we see that asthma/hay fever shows an imbalance between children with AD and the comparators, 5% vs. 14% at baseline and 16% vs. 49% at the end of the study, a fact that could explain the difference between the models for lower respiratory infections.

Many analyses were performed, which causes the multiple testing problem, i.e. yielding a higher risk of a false significant result than the targeted 5%. The authors used Bonferroni correction to adjust for this, i.e. lowering the significance level by dividing it by the number of tests. When highlighting statistically significant results rather than clinically relevant results, there is a need to discuss the risk of false positives.[6] For example, if 10 tests are performed, the risk of at least one false positive is about 40%.

The results might be affected by channelling, reverse causation and surveillance bias. In 'children treated with immunosuppressants have a thorough assessment that focuses, among other things, on infection risk before they are prescribed, and they also undergo repeated monitoring. These efforts likely minimize the risk in children with AD who are immunosuppressed, and even prevent their use in those who have higher baseline risk of severe infection', the authors describe channelling, i.e. informed selection of patients receiving a treatment. Selected patients might have lower baseline AD severity, affecting the risk of infections later, and surveillance bias from the repeated monitoring.[7] Moreover, 'Infections can trigger worsening of atopic dermatitis (AD)' describes reverse causation, i.e. the study outcome is the cause of the exposure.[8]

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