Atopic dermatitis: epidemiology & off-label therapy
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This thesis aims at unraveling some epidemiologic and treatment facets of atopic dermatitis (AD). To this end, we performed studies that focused on prevalence, diagnostic criteria, clinical outcome measures and off-label therapy of AD. This chapter will discuss the main findings of this thesis, puts it in the context of the current knowledge and presents recommendations for future research.

In the first part of this thesis (chapter 2), evidence concerning the urban/rural gradient in the prevalence of AD is summarized. As genetics alone cannot explain the rapid increase of the prevalence of AD in the last decades, environmental factors are also likely to play a role in the development of AD in an individual. We found evidence that indicated that AD is more prevalent in an urban than in a rural environment and thus urban lifestyle seems to be associated with a higher prevalence of AD. Which aspects of urban lifestyle are important should be subject of further research in which also time point and duration of exposure is included.

The second part of this thesis (chapter 3 & 4) aims at improving the diagnostic work-up as well as the outcome reporting on AD. The evidence on validity of diagnostic criteria is summarized in a systematic review, indicating the lack of uniformity in the use and lack of validity of some diagnostic criteria. Also, the millennium criteria were validated and refined. These criteria are especially aimed for hospital-based studies and enable sub-analysis by differentiating between atopic and atopiform dermatitis, which is a niche in the market. Concerning the outcome measures, we established the responsiveness of four clinical outcome measures, the Eczema Area and Severity Index, Patient-oriented Eczema Measurement and (objective) Severity Scoring of Atopic Dermatitis. Thereby, we have calculated the minimal clinically important difference. Based on this, accurate power calculations can be made and it can be decided if statistically significant differences reflect a real change in disease severity to deserve consideration in clinical practise.

In order to increase the impact of clinical research, it is inevitable to ensure adequate (and repeatable) diagnosis and outcome reporting. For both applies that many different tools are currently used and that most of them lack good methodological and clinimetric quality. This impairs the quality of evidence and disables comparison between studies, thereby prohibiting generating higher levels of evidence. As stated by Tugwell from the OMERACT initiative (Outcome Measures in Rheumatoid Arthritis Clinical Trials), ‘clinical trials are only as credible as their endpoints’; We would like to add ‘and as their diagnostic criteria’. In this light, harmonizing diagnostic criteria and clinical outcome reporting is of vital importance. Initiatives to establish consensus like HOME (Harmonizing
Outcome Measurement in Eczema) should be welcomed with enthusiasm by clinical researchers as well as by key players in the expert field.

Besides clinical severity outcome measures, biomarkers, when established as reliable outcome measures in future studies, could provide us with real objective measurement.

The third part of this thesis (Chapter 5) was aimed at off-label systemic therapy for AD. Physicians run out of treatment options for patients with severe AD as registered treatment options can be contra-indicated or fail. In the absence of new major developments for therapeutics that specifically targets severe AD, more general immunosuppressive drugs are focus of investigator-initiated research. In a randomized controlled trial, evidence was generated that showed that methotrexate and azathioprine are effective treatment options for severe AD and thereby we have expanded the evidence-based treatment armamentarium. Future studies should be performed to establish optimum dosages, to confirm the long-term safety profile of both methotrexate and azathioprine, to confirm their role in children and to compare both treatments with other therapies such as cyclosporin, oral corticosteroids and other disease modifying anti-inflammatory drugs.

In order to identify applicable off-label treatment options and to indicate new fields of research, available evidence for often off-label prescribed drugs should be summarized. We have provided a methodologically sound overview of two systemic drugs that have potential benefit in AD and some other recalcitrant skin diseases. Besides the need for long-term registries, those reviews are needed to provide evidence for guidelines to justify off-label therapy.

FUTURE CONSIDERATIONS
Without any doubt, a lot has changed over the last years concerning research in AD. It is a somewhat provocative comment to state that research in AD in the past years has been mostly dominated by a lack of uniformity, but not less true. However, times are changing and initiatives to harmonize are now put forward. Dermatologists worldwide seem to be more and more aware of the need to find consensus. If we want to proceed to generate high levels of evidence and thereby expanding our knowledge of the management of AD, it is conditional to combine our forces and clear the road.