## CLINICAL REPORT

# Prognosis after Hospitalization for Erythroderma

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Erythrodermic psoriasis (EP) and erythroderma exfoliativa (EE) are acute and potentially life-threatening inflammatory reactions. We estimated hazard ratios (HRs) of 3-year mortality following hospitalization for EP or EE compared with general population controls, patients hospitalized for psoriasis vulgaris, and toxic epidermal necrolysis (TEN), respectively. We identified 26 and 48 patients with a first-time hospitalization (1997–2010) for EP and EE, respectively (10 matched population-controls for each patient), 1,998 patients with psoriasis vulgaris, and 60 patients with TEN. During follow-up, 8 (30.8%) patients with EP, 19 (39.6%) patients with EE, and 34 (56.7%) patients with TEN died. Compared with population-controls, adjusted HRs were 4.40 (95% CI 1.66–11.70) for EP and 2.16 (1.21–3.82) for EE. Compared with psoriasis vulgaris, adjusted HRs were 1.83 (0.90–3.73) for EP, and 1.28 (1.01–1.63) for EE. The risk was significantly lower in EP (0.38 (0.16–0.91)) and in EE (0.50 (0.36–0.71)), compared with TEN. Mortality in EP and EE is high, and close follow-up is advised. *Key words: erythrodermic psoriasis; erythroderma; erythroderma exfoliative; mortality; risk; epidemiology.*

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Erythrodermic psoriasis (EP) and exfoliative dermatitis/erythroderma exfoliativa (EE) are acute, potentially life-threatening inflammatory dermatoses, collectively referred to as erythroderma. While they predominantly occur in men between the ages of 30 and 60 years (1, 2), the overall incidence of erythroderma among dermatology patients ranges from 0.01% to 0.04%, of which 25% cases are EP, i.e. related to underlying psoriasis (3, 4). In the pre-biologics therapy era, it was estimated that 1–2.25% of patients with psoriasis would develop EP, but data from recent years are lacking (4, 5). There are a number of known causes of EE, including drugs, malignancies (including cutaneous T-cell lymphoma), pityriasis rubra pilaris, and eczema, yet the aetiology remains obscure in a number of cases.

Clinically, erythroderma is characterized by inflammation involving all or most (>90%) of the body, with or without exfoliation. Aside from the distinctive erythema, symptoms may include fever, chills, malaise, lymphadenopathy, nail dystrophy, alopecia, and high output congestive heart failure (1, 2, 6–8). Moreover, patients may lose significant amounts of water, with the barrier defect accounting for up to 10% of daily water loss (9). Although patients with erythroderma are at increased risk of superinfections and sepsis, in particular from *Staphylococcus aureus* (8), systemic immunomodulating agents including prednisolone, cyclosporine, methotrexate, acitretin, and certain biologics are considered first-line treatment options (5).

While significant medical advances have occurred over the past 2 decades, erythroderma remains classified as a potentially fatal condition. However, remarkably little is known about the prognosis and mortality in these patients. We present data on the 3-year survival of all patients in Denmark (1997–2010) hospitalized with EP or EE, respectively.

## METHODS

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark.

The unique civil registration number assigned to each Danish resident at birth or on immigration allows for unambiguous linkage among all Danish population-based administrative and health registries (10). The universal Danish National Health Service provides tax-supported healthcare to all residents, with unrestricted access to hospitals. The Danish National Patient Register contains information on all patients admitted to Danish hospitals, including one primary and up to 19 secondary diagnoses coded by discharging physicians, according to the Danish version of the International Classification of Diseases, 10th revision (ICD-10) (11). The primary diagnosis is the main reason for hospitalization, and secondary diagnoses are additional conditions, including complications. Within 14 days of death, all deaths and causes of deaths are accurately recorded in the National Causes of Death Registry using ICD-10 codes (12).

From the Danish National Patient Registry we identified all patients from 1 January 1997, through 31 December 2010, with a first-time (inpatient) hospitalization with EP (primary ICD-10 codes L40.0A and L40.8B) or EE (primary ICD-10 codes L26.9A and L53.8C) as the primary cause of admission. No patients younger than 35 years of age were hospitalized with the aforementioned diagnoses during the study period. Each patient was matched on age, sex, and date of admission, to 10 controls from the general population. In addition, we identified all patients aged ≥35 years with a first-time (inpatient) hospitalization for psoriasis vulgaris (primary ICD-10 code L40.0),

or toxic epidermal necrolysis (TEN) (primary ICD-10 code L51.2). We have previously examined the medical records of 50 randomly selected patients consecutively referred for first-time hospital-based treatment of psoriasis vulgaris, albeit in an outpatient setting. The majority of patients were actively treated with topical agents when evaluated and presented with a mean Psoriasis Area and Severity Index (PASI) score of 10, which was consistent with severe psoriasis (13). Similarly, in a recent study examining all ($n=250$) patients from 2 Danish hospitals diagnosed with erythema multiforme, Stevens-Johnson syndrome, and TEN, respectively, the TEN diagnosis was confirmed with a specificity of 100% (14).

Patients were followed 3 years from the date of first hospitalization (study start), or until death, whichever came first. Comorbidity up to 5 years before study start was classified using the Charlson Comorbidity Index, which summarizes 19 conditions found to have a prognostic effect. Use of the Charlson Comorbidity Index in the Danish National Patient Register has an overall positive predictive value of 98% (15) and, based on this score, patients were categorized into 3 comorbidity levels (0, normal; 1, moderate; and ≥2, severe). From Statistics Denmark we used information on tax-reported household income. This was used to calculate an age-standardized index of socioeconomic status between 0 (lowest group) and 4 (highest group) based on the mean gross annual income during a 5-year period before study start. Collection of data on smoking history and alcohol abuse has been described elsewhere (16, 17). The Strengthening the Reporting of Observational Studies in Epidemiology recommendations were used for conduct and reporting of this study (18).

*Statistical analysis*

We described baseline characteristics with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. We used Kaplan–Meier plots and log-rank tests for non-parametric estimation of the 3-year mortality. Event rates were calculated per 10 person-years, and Cox proportional hazard models were used to estimate crude and adjusted (adjusted for age, sex, socioeconomic status, smoking, alcohol abuse, and the Charlson Comorbidity Index score) hazard ratios (HRs) with 95% confidence intervals (CI). Model assumptions were tested and found to be valid. $p$-values $<0.05$ were considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 11.2 (Stata-Corp, College Station, TX, USA) were used for data analysis.

RESULTS

Between 1 January 1997 and 31 December 2010, we identified a total of 26 and 48 patients admitted for hospital-based treatment of EP and EE, respectively, and 260 and 480 matched controls from the general population. Similarly, we found 60 and 1,998 patients admitted due to TEN and psoriasis vulgaris, respectively. Across the groups there was a male predominance, except for TEN, which occurred slightly more frequently in women. The baseline characteristics are shown in Table I.

There were no erythroderma patients with a pre-existing diagnosis of drug-induced exanthema, but 6 patients with EE had previously been diagnosed with malignant neoplasms of lymphoid, haematopoietic, or related tissues (ICD-10 codes C81–C96). Fig. 1 shows the non-parametric Kaplan–Meier survival curves ($p<0.0001$ for trend), and during the 3-year follow-up, 30.8% (8/26) of patients with EP and 7.7% (20/260) of their age- and sex-matched general population controls died. Similarly, 39.6% (19/48) of patients with EE and 14.2% (68/480) of their controls died, while death occurred in 13.6% (272/1998) of patients with psoriasis vulgaris, and 56.7% (34/60) of patients with TEN (Table II). Cox regression in patients with EP revealed adjusted HRs with 95% CI of 4.40 (1.66–11.70) vs. general population controls, 1.83 (0.90–3.73) vs. psoriasis vulgaris, and 0.38 (0.16–0.91) vs. TEN. In patients with

Table I. *Baseline characteristics of the study population*

| | Erythrodermic psoriasis | | Erythroderma exfoliativa | | Controls | |
| --- | --- | --- | --- | --- | --- | --- |
| | Cases ($n=26$) | General population controls ($n=260$) | Cases ($n=48$) | General population controls ($n=480$) | Psoriasis vulgaris ($n=1,998$) | Toxic epidermal necrolysis ($n=60$) |
| Age, years, mean (SD) | 60.9 (14.6) | 60.9 (14.6) | 74.3 (9.7) | 74.3 (9.7) | 57.5 (13.1) | 65.5 (15.6) |
| Women, *n* (%) | 6 (23.1) | 60 (23.1) | 16 (33.3) | 160 (33.3) | 866 (43.3) | 33 (55.0) |
| Men, *n* (%) | 20 (76.9) | 200 (76.9) | 32 (66.7) | 320 (66.7) | 1132 (56.7) | 27 (45.0) |
| Ethnic origin, *n* (%) | | | | | | |
| Danish | 26 (100) | 246 (94.6) | 48 (100) | 454 (94.6) | 1910 (95.6) | 60 (100) |
| Other | 0 (0) | 14 (5.4) | 0 (0) | 26 (5.4) | 88 (4.4) | 0 (0) |
| Socioeconomic status, mean (SD)[a] | | | | | | |
| vs. general population controls | 1.2 (1.7) | 2.1 (1.4) | 1.9 (1.4) | 2.0 (1.4) | N/A | N/A |
| vs. psoriasis vulgaris | 1.5 (1.3) | N/A | 1.4 (1.4) | N/A | 2.0 (1.4) | N/A |
| vs. toxic epidermal necrolysis | 1.9 (1.5) | N/A | 1.7 (1.4) | N/A | N/A | 2.4 (1.3) |
| Smoking, *n* (%) | 7 (26.9) | 29 (11.2) | 16 (33.3) | 64 (13.3) | 451 (22.6) | 14 (23.3) |
| Alcohol abuse, *n* (%) | 4 (15.4) | 5 (1.9) | 4 (8.3) | 5 (1.0) | 167 (8.4) | 6 (10.0) |
| Charlson Comorbidity Index | | | | | | |
| Normal (0) | 16 (61.5) | 220 (84.6) | 25 (52.1) | 404 (84.2) | 1,391 (69.6) | 28 (46.7) |
| Moderate (1) | 6 (23.1) | 23 (8.9) | 10 (20.8) | 41 (8.5) | 289 (14.5) | 7 (11.6) |
| Severe (≥2) | 4 (15.4) | 17 (6.5) | 13 (27.1) | 35 (7.3) | 318 (15.9) | 25 (41.7) |

[a]Socioeconomic status is calculated as an age-standardized index between 0 (lowest group) and 4 (highest group) based on the mean gross annual income during 5-year period before study start. The mean socioeconomic status is relative to the comparison groups, hence 3 different values for EE and EP cases.
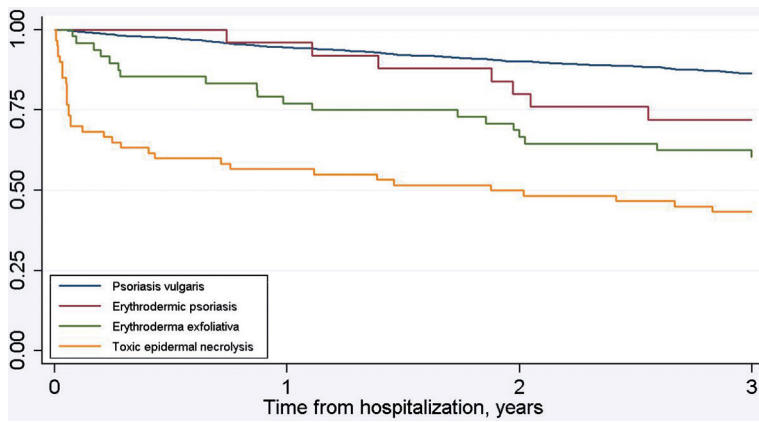SD: standard deviation; N/A: not applicable.

**Fig. 1.** Kaplan–Meier plot of the 3-year survival in patients with psoriasis vulgaris, erythrodermic psoriasis, erythroderma exfoliativa, and toxic epidermal necrolysis, respectively.

EE, the adjusted HRs were 2.16 (1.21–3.82) vs. general population controls, 1.28 (1.01–1.63) vs. psoriasis vulgaris, and 0.50 (0.36–0.71) vs. TEN (Table III). In patients with EP and EE, deaths were predominantly due to major adverse cardiovascular events and cancer (approximately 45% of malignancies were lymphomas).

## DISCUSSION

In this population-based cohort study 30.8% and 39.6% of patients with EP and EE, respectively, died within the first 3 years following hospital admission, whereas 13.6% of patients with severe psoriasis vulgaris, and 56.7% of patients with TEN died, respectively, following admission. The high 3-year mortality in patients with EE and EP, underscores the need for close follow-up and management of comorbidities in previously hospitalized patients.

Previous data on mortality in patients with erythroderma is scarce and limited to reports dating back more than 25 years (4, 6, 7, 19, 20). Boyd & Menter (4) reported that, during a mean follow-up of 33.5 months (range 6–88), 4% of patients with EP who had been seen in their outpatient clinic (1979–1987) died. In 1963, Abrahams et al. (7) reported an 18% mortality rate in EE, whereas Wilson (20) in 1954 stated that 39% of his patients had died from complications owing to EE.

In 1973, Nicolis & Helwig (6) described a mortality rate of 64% in EE, while Thestrup–Pedersen (19) in 1988 noted that half of Danish patients from a single hospital diagnosed in the course of 15 years with EE of unknown aetiology had died during the observation period.

However, within the last 2 decades, significant advances have been made in emergency hospital care, and the advent of newer systemic agents, such as anti-tumour necrosis factor-α and anti-interleukin 12/23 agents, have significantly broadened the therapeutic options for patients, in particular those with psoriatic disease including EP. Nonetheless, we found high mortality rates that were comparable with results from much older studies (4, 6, 7, 19, 20). Explanations may include poor treatment adherence in these patients or a stronger effect of risk factors. As indicated by our results, patients with EP and EE have a lower socioeconomic status and a higher prevalence of comorbidities, smoking, and alcohol abuse than their general population and psoriasis controls. Therefore, we also used patients admitted for hospitalized-based treatment of psoriasis vulgaris or TEN as control groups, and results from these analyses underline the high-risk population posed by patients with erythroderma. Notably, while death from TEN usually occurs shortly after diagnosis, the 3-year mortality of EE in our study was comparable to the short-term mortality rate in patients with TEN, as indicated by the Kaplan–Meier survival curves (see Fig. 1).

Our study was strengthened by the high accuracy of the Danish registries, ensuring complete follow-up and prospectively recorded information on, for example, comorbidity and tax-reported income ensured that recall bias was virtually eliminated. However, while we used nationwide data, the absolute number of patients was low and was limited to those requiring inpatient hospital treatment for EP and EE, and results should

**Table II.** *Summary of follow-up time, number of deaths, and event rates per 10 person-years*

| | Person-years | Deaths n (%) | Rate per 10 person-years 95% CI |
|---|---|---|---|
| Erythrodermic psoriasis | 66.2 | 8 (30.8) | 1.21 (0.60–2.42) |
| Controls (general population) | 748.9 | 20 (7.7) | 0.27 (0.17–0.41) |
| Erythroderma exfoliativa | 107.9 | 19 (39.6) | 1.76 (1.12–2.76) |
| Controls (general population) | 1,321.8 | 68 (14.2) | 0.51 (0.41–0.65) |
| Controls (psoriasis vulgaris) | 5,548.5 | 272 (13.6) | 0.49 (0.44–0.55) |
| Controls (TEN) | 97.6 | 34 (56.7) | 3.49 (2.49–4.88) |

CI: confidence interval; TEN: toxic epidermal necrolysis.

**Table III.** *Crude and adjusted hazard ratios (HR) of all-cause mortality in patients with erythrodermic psoriasis, and erythroderma exfoliativa*

| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR[a] (95% CI) | *p*-value |
|---|---|---|---|---|
| Erythrodermic psoriasis | | | | |
| vs. general pop. | 4.54 (2.00–10.31) | 0.0003 | 4.40 (1.66–11.70) | 0.0003 |
| vs. PV | 2.45 (1.21–4.94) | 0.0126 | 1.83 (0.90–3.73) | 0.0933 |
| vs. TEN | 0.39 (0.18–0.84) | 0.0169 | 0.38 (0.16–0.91) | 0.0294 |
| Erythroderma exfoliativa | | | | |
| vs. general pop. | 3.37 (2.03–5.61) | <0.0001 | 2.16 (1.21–3.82) | 0.0087 |
| vs. PV | 1.88 (1.49–2.38) | <0.0001 | 1.28 (1.01–1.63) | 0.0448 |
| vs. TEN | 0.73 (0.55–0.97) | 0.0297 | 0.50 (0.36–0.71) | 0.0001 |

[a]Adjusted for age, sex, socio-economic status, smoking, alcohol, and the Charlson Comorbidity Index score.
CI: confidence interval; HR: hazard ratio; pop.: population; PV: psoriasis vulgaris; TEN: toxic epidermal necrolysis.

be interpreted accordingly. Also, we cannot exclude the possibility that residual confounding may have affected our estimates. In addition, all of our patients were of Danish origin, i.e. Caucasian decent, but while erythroderma have been reported previously in a limited number of patients with darker skin (4, 6, 7), extrapolation of our results to such individuals may be limited. Lastly, while the majority of deaths were due to cardiovascular disease and malignancies, whether these deaths were directly attributable to erythroderma remains unknown.

In conclusion, we found a high 3-year mortality rate in patients with EP and EE. These patients pose a high-risk population with excess of comorbidities and low socioeconomic status, and we recommend that they are closely followed with focus on modifiable risk factors.

## ACKNOWLEDGEMENTS

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