Understanding Epidermal Necrolysis after the Initial Hospitalization

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In-hospital mortality for epidermal necrolysis (EN) has been well-characterized, but less is known about the long-term complications. Marxer et al. (2020) report mortality rates of 7.4% during the initial hospitalization, 4.8% within 90 days, and 7.6% after 91 days. Compared with that of matched controls, long-term mortality was not increased, highlighting the importance of understanding the long-term sequelae of EN survivors.


Epidermal necrolysis (EN), encompassing the spectrum of Stevens–Johnson syndrome (SJS) and toxic EN (TEN), is a rare, adverse drug reaction associated with significant morbidity and mortality during the initial hospitalization. The majority of research to date has focused on understanding the pharmacogenetics, prognosis, and treatment effects during the initial hospitalization. Little is known about the prevalence and management of long-term sequelae, including mortality. Using two separate population-based databases from Britain, Marxer et al. (2020) examine both short-term and long-term mortality in patients diagnosed with EN. The authors report an increased risk of mortality in the first 90 days after an EN diagnosis, but after 90 days, the risk of death returns to baseline (Marxer et al., 2020).

Clinical research on rare, life-threatening diseases is often challenging. Retrospective, single-institution studies often lack power owing to small sample sizes and are limited by incomplete or inconsistent reporting of information in medical records. A larger sample size is typically available in administrative claims datasets, but information about disease severity is unavailable. In addition, previous validation studies have shown that EN diagnoses codes alone cannot accurately identify patients, creating a potential for misclassification bias (Eisenberg et al., 2012). Finally, studies using cohorts from referral centers or disease-specific registries may lack less severe cases, creating questions about the generalizability of the results.

The use of two population-based data sources to separately assess short- and long-term mortality is a major strength of this study. To examine the short-term mortality, the authors used the Hospital Episode Statistics Admitted Patient Care dataset, which contains information on all admissions at National Health Service hospitals in England and captures 98–99% of total hospitalizations. Long-term mortality was examined in The Clinical Practice Research Datalink (CPRD) GOLD, a longitudinal, population-based dataset with complete patient information from a network of general practitioners practices across the United Kingdom. CPRD GOLD contains information about all healthcare encounters and is generally representative of occurrences in the United Kingdom population (Herrett et al., 2010). In CPRD, an SJS and/or TEN diagnosis has been previously validated to have a high positive predictive value (87%) (Frey et al., 2017).

In modern multisite or national cohorts, the in-hospital mortality in patients with EN ranges from 15% to 25% (Micheletti et al., 2018; Sekula et al., 2013; Sousa-Pinto et al., 2018). Marxer et al. (2020) report an in-hospital mortality rate of 7.4% among patients hospitalized in England. The reason for the lower rate seen in this study is likely due to several factors. The use of population-based data likely includes the full spectrum of disease severity and is not biased toward severe cases cared for at referral centers. Other factors that may decrease mortality, including differences in supportive care and in treatment effects of immunomodulatory therapies, cannot be specifically calculated in this study. One of the major knowledge gaps in EN is the lack of information about the ability of immunomodulatory therapies to improve patient outcomes.

Few studies have examined mortality in patients with a history of EN after the initial hospitalization. Using a population-based longitudinal dataset from the United Kingdom, the authors report mortality rates of 4.8% (95% confidence interval [CI] = 4.4–5.2) within 90 days after EN diagnosis and 7.6% (95% CI = 5.2–10.0) between day 91 and the end of the follow-up period, with a maximum follow up of 5 years. In the multinational RegiScar cohort, a mortality rate of 23% (95% CI = 19–27) was reported within 6 weeks of diagnosis and 34% (95% CI = 30–39) after 1 year (Sekula et al., 2013). The factors that account for the lower rates of long-term mortality in this population-based study are likely similar to the factors discussed regarding short-term mortality.

Finally, Marxer et al. (2020) used propensity score matching to compare the long-term mortality in patients with a history of EN with that of matched patients without a history of EN. After matching patients on the basis of demographics, lifestyle factors, healthcare utilization, and health comorbidities, no increased risk of death was seen after day 90 (hazard ratio = 0.80, 95%
Clinical Implications

- In-hospital mortality was 7.4% in this population-based cohort from England.
- Mortality after 91 days was not increased above the baseline rates.
- Additional research is necessary to understand the long-term sequelae.

CI = 0.55–1.16) (Marxer et al., 2020). This confirms what was previously reported from the RegiScar cohort. EN disease severity was associated with an increased risk of death in the first 90 days after diagnosis but not after 90 days (Sekula et al., 2013).

Given the mortality associated with EN, previous clinical research has focused on improving the care of patients during the initial phase, but preliminary research suggests that many patients experience long-term morbidity. In addition to the cutaneous and mucous membrane (ocular, oral, and genitourinary) sequelae, pulmonary, renal, autoimmune, and psychiatric long-term complications have been reported (Lee et al., 2017; Wang et al., 2020; Yang et al., 2016). Cutaneous and ocular complications were reported in 44% of Taiwanese EN survivors (Yang et al., 2016). A retrospective review of EN survivors from the United States identified long-term sequelae in the medical records of 45.3% of patients (Wang et al., 2020), likely underestimating the true incidence. Finally, when EN survivors were assessed with psychological and health-related QOL questionnaires, 65% had symptoms of post-traumatic stress and 29% had scores on psychological and health-related QOL instruments consistent with clinical signs of possible post-traumatic stress disorder (Dodiuk-Gad et al., 2016). These small studies suggest ongoing morbidity in patients with a history of EN that extends well beyond the initial hospitalization.

In conclusion, Marxer et al. (2020) report mortality rates of 7.4% during the hospitalization, 4.8% within 90 days, and 7.6% after 91 days and that mortality risk returns to baseline rates 90 days after an EN diagnosis. This study adds important information to the literature by providing population-based estimates of both short-term and long-term mortality in patients with EN. In addition to the continued work to understand the genetic risk factors, pathophysiology, and treatment effects of immunomodulatory therapies, additional research is necessary to understand the long-term sequelae of EN and develop evidence-based treatment plans to reduce morbidity for these patients.

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CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES