Incidence of Epidermal Necrolysis: Results of the German Registry


TO THE EDITOR

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions resulting in wide-spread epidermal detachment and erosions of mucous membranes. They are considered as severity variants sharing the same pathogenesis and etiology and are, therefore, referred to as epidermal necrolysis (EN) (Mockenhaupt and Roujeau, 2019). Clinically, severity is distinguished on the basis of the amount of skin detachment: SJS < 10%, SJS/TEN overlap of 10–30%, and TEN > 30% (Bastuji-Garin et al., 1993a). Mortality during hospital stay can increase to >40% in TEN (Mockenhaupt and Roujeau, 2019). Most often, EN occurs during the one month of the first exposure to a new drug (Mockenhaupt et al., 2008). Nevertheless, in about 25% of all cases, no culprit drug can be determined (Paulmann and Mockenhaupt, 2017). EN is a very rare reaction with estimated incidences between one and six cases per million inhabitants per year reported for different countries in Europe (Diphoorn et al., 2016; Frey et al., 2017; Rzany et al., 1996).

The Dokumentationszentrum schwerer Hautreaktionen (dZh) is the ongoing German Registry of severe skin reactions founded in 1990 (Supplementary Material S1). It aims to collect data from all hospitalized patients with EN to provide reliable data on incidences in Germany and for assessment of risk factors such as drugs. To ensure diagnostic certainty, each case is rigorously reviewed by an independent expert committee on the basis of consensus definition (Bastuji-Garin et al., 1993a). Although limited to West Germany until 1995, the registry could already provide incidence estimates between 1.17 and 1.89 cases per 1 million inhabitants per year for EN in 1990–1992 (Rzany et al., 1996). As of now, the dZh has collected data of several thousands of new cases in Germany. The aims of this study are to describe ascertained cases with EN from 2003 to 2012 and provide an update on incidence estimates for Germany.

From 2003 to 2012, altogether 2,937 cases of potential severe cutaneous adverse reactions were reported to the dZh, of which 760 cases were validated as definite, probable, and possible cases of EN (Figure 1). Besides clinical data, the evaluation of diagnosis was based on relevant photographs and results of skin biopsies that were available in 93% and 76% of the patients, respectively (overlap 71%). As a result, the percentage of probable and definite cases was high (90%). A total of 229 (30%) patients developed the reaction while already hospitalized for another condition.

More women (61%) than men and more older people were affected, a finding that is already known from prior studies (Bastuji-Garin et al., 1993b; Diphoorn et al., 2016; Roujeau et al., 1990; Yang et al., 2016) and is usually explained by sex- and age-related differences in pharmacokinetics, hormonal, and immunologic factors and differences in medication use (Rademaker, 2001). Moreover, the proportion of younger patients (<40 years) increased with disease severity (SJS, 20%; SJS/TEN overlap, 22%; TEN, 35%). Although TEN has been described among young patients, studies within age groups are rare (Roujeau et al., 1990; Yang et al., 2016).

The in-hospital mortality was 28% and varied from 13% in SJS to 43% in SJS/TEN overlap and 49% in TEN. It also increased clearly with age from 6% in ≤11-year-old patients to 43% in ≥80-year-old patients and was especially high for TEN in the group of ≥65-year-old patients (68%, 26 of 38). Although a comparison of mortality data from previous European studies is hampered, reported mortality data ranging between 19.7% and 34% and increasing with patients’ age and severity of the reaction are quite consistent (Bastuji-Garin et al., 1993b; Diphoorn et al., 2016; Revuz et al., 1987; Schöpf et al., 1991).

The evaluation of causative drugs (Supplementary Material S2) revealed that an exposure in the relevant period to at least one drug with a previously reported high relative risk for EN (Mockenhaupt et al. 2008) was found in 50% of the patients. The three most frequently observed substances were allopurinol, sulfamethoxazole, and lamotrigine (Supplementary Table S1). Thus, allopurinol still remains the most common cause of EN in Germany, as already demonstrated for several European countries (Halevy et al., 2008; Mockenhaupt et al., 2008). In contrast to in-hospital acquired cases, the percentage of exposure to high-risk drugs was higher in community-acquired cases (76%; reactions that occurred in a patient’s normal surrounding and not in the hospital). Whereas 49% of the patients have either been exposed to high-risk drugs outside the relevant period (beginning of drug use within 8 weeks and use of drug in the 2 weeks before reaction onset) or have been exposed to drugs without a high risk for EN, no drug exposure at all was observed in 1% of the patients.

Using German population data from 2003 to 2012 (Supplementary Material S3), the overall incidence rate for EN...
was 0.93 cases per 1 million individuals per year (95% CI = 0.86–1.00; Table 1 and also see Supplementary Table S2 for more details). With respect to the severity of the reactions, the incidence in Germany was highest for SJS and lowest for TEN. Because more patients were female, the overall incidence rate for women was clearly higher than for men (1.11 vs. 0.74). Furthermore, incidence rates increased with age. Although the overall incidence of EN among patients aged <12 years was rather low, they were affected by higher severity of the reaction.

In comparison with the prior study conducted by the dZh, the incidence rate and the average number of validated cases per year registered by the dZh have decreased (Rzany et al., 1996). This is certainly a consequence of more rigorous case validation and a more than three times longer-study period (1990–1992 vs. 2003–2012). Because we cannot rule out that changes in drug consumption may play a role and that a small number of cases may be missed by the dZh, we evaluated case ascertainment by the dZh in more detail (Supplementary Material S4). Although this could only be indirectly addressed, data do not indicate major changes in the work of the dZh over time.

When comparing our incidence results with those of other studies in Europe, reported incidences for EN are often higher than those of this study’s analysis. In contrast to the prospective approach of the dZh, studies reporting highest incidence rates were studies with retrospective case ascertainment, for example, 5.19 cases per 1 million individuals per year for Spain and 5.76 cases for the United Kingdom (Frey et al., 2017; Velasco-Tirado et al., 2018). However, in these two studies, cases had been identified from healthcare databases lacking the possibility of rigorous case validation and thus were prone to misclassification and over-estimation of incidences.

In conclusion, the dZh was able to successfully collect data on EN in Germany through a nationwide prospective ascertainment approach in combination with rigorous case validation. Based on data obtained in this 10-year period, reliable estimates of incidence rates for EN could be provided. Although incidence rates slightly decreased compared with previous results, additional evaluation does not suggest that a larger number of cases were missed.

Data availability statement
Owing to legal and ethical reasons, data cannot be made publicly available. Upon request, analysis data are available from the corresponding author.

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CONFLICT OF INTEREST
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Figure 1. Flowchart of case ascertainment of EN by the dZh in Germany (2003–2012). AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; dZh, Dokumentationszentrum schwerer Hautreaktionen; EEMM, erythema exsudativum multiforme majus; EN, epidermal necrolysis; GBFDE, generalized bullous-fixed drug eruption.
Table 1. Estimated Annual Incidence Rate of EN Per 1 Million Inhabitants in Germany

<table>
<thead>
<tr>
<th>Overall</th>
<th>SJS</th>
<th>SJS/TEN Overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases in total</td>
<td>818,411,119</td>
<td>0.93 (0.86–1.00)</td>
<td>(760)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD) 57.4 (22.4)</td>
<td></td>
<td></td>
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<tr>
<td>0–11</td>
<td>88,169,337</td>
<td>0.36 (0.25–0.51)</td>
<td>(32)</td>
</tr>
<tr>
<td>12–18</td>
<td>60,224,819</td>
<td>0.38 (0.24–0.57)</td>
<td>(23)</td>
</tr>
<tr>
<td>19–64</td>
<td>507,352,193</td>
<td>0.66 (0.60–0.74)</td>
<td>(337)</td>
</tr>
<tr>
<td>65–79</td>
<td>123,116,751</td>
<td>2.02 (1.78–2.29)</td>
<td>(249)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>39,548,019</td>
<td>3.01 (2.49–3.60)</td>
<td>(119)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>417,774,513</td>
<td>1.11 (1.01–1.22)</td>
<td>(465)</td>
</tr>
<tr>
<td>Male</td>
<td>400,636,606</td>
<td>0.74 (0.66–0.83)</td>
<td>(295)</td>
</tr>
</tbody>
</table>

Abbreviations: EN, epidermal necrolysis; N cases, number of cases/frequency; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

1Population data for the same period were obtained from the German Federal Institute for Statistics.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.03.968.

REFERENCES


