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The Seven-Fold Rise in Incidence of Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis: Associations with COVID-19 and the Vaccine

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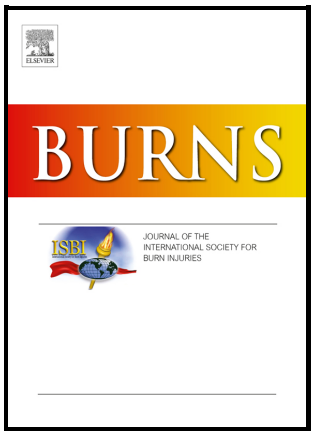

PII: S0305-4179(23)00128-6

DOI: https://doi.org/10.1016/j.burns.2023.06.016

Reference: JBUR6942

To appear in: *Burns*

Please cite this article as: Edward A Stanley, Lois Zhang, Justine O'Hara, Peter Haertsch and Peter Maitz, The Seven-Fold Rise in Incidence of Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis: Associations with COVID-19 and the Vaccine, *Burns,* (2023) doi:https://doi.org/10.1016/j.burns.2023.06.016

Title: The Seven-Fold Rise in Incidence of Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis: Associations with COVID-19 and the Vaccine

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Abstract

Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) is a rare, potentially life threatening mucocutaneous hypersensitivity reaction resulting in desquamation of the skin and mucosa. These patients are managed on burns units due to the widespread desquamation.

We report the largest case series of participants developing SJS/TEN in the setting of recent COVID infection or vaccination. We found a seven-fold increase in SJS/TEN since the COVID pandemic. This increase correlates with an increase in COVID infections and vaccination rates. We explore the immunopathological relationships between COVID and SJS/TEN and propose theories for possible associations.

Key words: COVID-19, Stevens-Johnson syndrome, toxic epidermal necrolysis

Background

Medical conditions secondary to COVID are still being defined. As COVID case numbers continue to rise, there too is a rise in conditions once deemed rare. We present the largest case series of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) which may be associated with COVID or the vaccine. This case series provides the framework for exploring possible immunological pathways linking COVID and the development of SJS/TEN.

SJS/TEN is a rare, potentially life threatening mucocutaneous delayed hypersensitivity reaction (1). It involves desquamation of the epidermis and mucosa. It is often drug related although may be triggered by infections. SJS/TEN is classified based on its percentage total body surface area (%TBSA) desquamation. SJS is less than 10% TBSA, overlap SJS/TEN 10-30% TBSA and TEN > 30% TBSA (2). The estimated incidence is 1.6 (for SJS) – 9.2 (for TEN) cases per million per year worldwide (3) with a mortality rate of over 40% in severe cases (4).

SJS/TENS pathophysiology

SJS/TEN is triggered through a T-cell mediated response. Although the exact mechanism remains unclear, the implicated pathways are thought to be via a granule-mediated exocytosis or via a Fas-Fas ligand apoptosis cascade (5) (6). Studies suggest that in the granule-mediated pathway, cytotoxic T cells and natural killer cells exocytose perforin, granulysin and granzyme B which cause keratinocyte damage (7) (8). Perforin, granzyme B and granulysin have been found in early blister

fluid and their concentrations may correlate with disease severity (9). In the Fas-Fas ligand pathway, Fas ligand is secreted by lymphocytes and binds to a Fas death receptor expressed by keratinocytes causing keratinocyte apoptosis (10).

COVID pathophysiology

The SARS-CoV-2 virus is responsible for COVID. It is postulated that the spike protein of the virus binds to the ACE-2 receptor on pulmonary epithelial cells (11). This leads to a conformation change of the epithelial cell membrane allowing viral penetration into the cell. The cell's endoplasmic reticulum is hijacked leading to viral replication. New viral particles are transported to the cell membrane via Golgi vesicles and released by exocytosis.

Case series

In 2022, our institution saw a sharp rise in SJS/TEN presentations. As a state-wide burns unit and referral centre for SJS/TEN, our institution manages two to four cases per year, prior to COVID. In the first six months of 2022 however, we managed fourteen cases. Five of these cases had COVID in the preceding month. Three of the fourteen had a COVID vaccine in the preceding month. All fourteen cases received a COVID vaccine.

We present a case series of eight patients diagnosed with COVID or having received the vaccine in the preceding month. All data collected was de-identifiable with all

authors having access. Ethics approval was not required due to negligible risk. No funding was required with no conflicts of interest to declare.

Case 1

A 60-year-old female admitted with 55% TBSA TEN (figure 1). COVID infection six weeks prior to onset. Received allopurinol for exacerbation of gout. Has previously taken allopurinol with no adverse effect. She was double vaccinated with a mRNA vaccine.

Case 2

A 78-year-old female admitted with 60% TBSA TEN. COVID five weeks prior to onset. Developed COVID associated pneumonitis and received piperacillin/tazobactam. She was double vaccinated with a mRNA vaccine.

Case 3

A 54-year-old female admitted with 40% TBSA TEN. COVID four weeks prior to onset. Developed COVID associated pneumonitis secondary to aspergillus. Received voriconazole. She was double vaccinated with a mRNA vaccine.

Case 4

A 26-year-old male admitted with 70% TBSA TEN. Received a mRNA vaccine three weeks prior to onset. Due to vaccine associated symptoms, he took paracetamol and ibuprofen. He has previously taken paracetamol and ibuprofen with no adverse effect. He was triple vaccinated with previous two doses of a viral vector vaccine.

Case 5

A 45-year-old-male admitted with 70% TBSA TEN. COVID infection four weeks prior to onset. Received levetiracetam for seizure prophylaxis post a traumatic subarachnoid haemorrhage. He was triple vaccinated with a mRNA vaccine.

Case 6

A 53-year-old-female admitted with 95% TBSA TEN. Received a viral vector vaccine three weeks prior to onset. Quadruple vaccinated with previous doses of both viral vector and mRNA vaccines. Received captopril and amlodipine for scleroderma renal crisis.

Case 7

A 47-year-old male admitted with 10% TBSA SJS/TEN overlap. COVID infection five weeks prior to onset. Received amoxycillin four weeks prior. Has previously taken amoxycillin with no adverse effect. Triple vaccinated with mRNA vaccine.

Case 8

A 53-year-old female admitted with 90% TBSA TEN. Received a mRNA vaccine four weeks prior to onset. Triple vaccinated with mRNA vaccine. Received piperacillin/tazobactam for bacterial peritonitis. Has previously taken penicillins with no adverse effects.

Discussion

This is the largest case series exploring possible associations between COVID, the vaccine and SJS/TEN.

The first case of COVID in Australia was diagnosed on 25 January 2020. By the end of 2020, there were approximately 28,500 cases of COVID in the country with 4,928 reported cases in our state (New South Wales). Case numbers remained low in the state in 2022, compared to world standards, with 182,576 new cases (figure 2). A rapid rise in cases began in January 2022 (figure 3). The first 6 months saw 7,627,874 new cases reported. We expect that these case numbers are under reported due to asymptomatic COVID infections, some infected individuals not seeking testing and not reporting positive rapid antigen test results. This under reporting is supported by the literature demonstrating a 40.5% global asymptomatic rate of COVID positive infections (12). We also saw a rapid rise in vaccination rates from January 2022 (figure 4).

We observed 14 cases of SJS/TEN in a six-month period, seven times the incidence prior to COVID. The rarity of SJS/TEN makes causality from COVID or the vaccine difficult to prove, especially in the setting of concomitant medications known to trigger the disease. However, the rapid increase in incidence since the pandemic and vaccination is alarming.

We propose three theories for the sudden rise in SJS/TEN case numbers.

1. Virus induced

The SARS-COV-2 virus may directly bind to receptors that trigger a T cell mediated response and subsequently SJS/TEN. Many viruses have already been implicated in

the development of SJS/TENS including herpes simplex virus, Epstein-Barr virus (EBV), cytomegalovirus and influenza (13). Their viral proteins bind to the major histocompatibility (MHC) complex I on the antigen presenting cell triggering activation of cytotoxic T cells. This T cell mediated response may subsequently result in SJS/TEN. Five cases of COVID infection preceding SJS/TEN have been reported in the literature (14) (15) (16) (17) (18) . The average time of onset from diagnosis was 3 weeks (range: 1 – 5 weeks). This is consistent with our cases with an average of 5 weeks (range: 4 – 6 weeks).

2. Vaccine induced

The vaccine may directly bind to receptors to trigger SJS/TEN. Many drugs, like viruses, have been implicated as triggers. It is recognised that drugs bind MHC class I to trigger a cytotoxic T cell response (5). A recent study found the ChAdOx1 nCoV-19 adenoviral vector vaccine induces T helper type 1 cells leading to clonal expansion of cytotoxic T cells and subsequent protection against severe COVID infection (19). This T cell response can also induce the granule mediated pathway of perforin, granulysin and granzyme B release to cause keratinocyte apoptosis seen in SJS/TEN. This response peaks between seven- and 28-days post vaccination (19). This time peak is consistent with our cases. Eight case reports have been identified in the literature describing SJS/TEN post-COVID vaccine. Four of these cases were associated with mRNA vaccines, three with viral vector vaccines and one with whole virus vaccines. In our case series, two patients received a mRNA vaccine and one a viral vector in the preceding month to their presentation.

3. Threshold lowering

The SARS-COV-2 virus or vaccine may lower the threshold for a drug to trigger SJS/TEN. We hypothesise that the virus or vaccine “primes” the immune system for a drug to cause SJS/TEN, which may not have done so without this “priming”. Infectious mononucleosis caused by EBV has this “priming” effect to induce a drug induced hypersensitivity (DiHS) reaction when an individual is exposed to penicillin. This DiHS manifests as a generalised rash. The large expansions of activated EBV-specific cytotoxic T cells and increased natural killer (NK) cell numbers are observed during the disease (20) and EBV-specific T cells have been shown to cross-react with self-human leukocyte antigen alleles (21) (22). The development of a drug rash during infectious mononucleosis may be due to cross reactivity between penicillins and the expansion of EBV- specific cytotoxic T cells already present prior to giving the drug.

Conclusion

This study identifies possible associations between COVID, the vaccine and the development of SJS/TEN. Our institution experienced a sudden rise in SJS/TEN case numbers in conjunction with a sudden rise in COVID infections (figure 3). We propose three theories for this seven-fold increase in case number; a virus induced, a vaccine induced and a threshold lowering pathway. We advise future research

investigates the impact viruses such as SARS-COV-2 have on immune mediated diseases such as SJS/TEN.

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Figure 1. Toxic epidermal necrolysis

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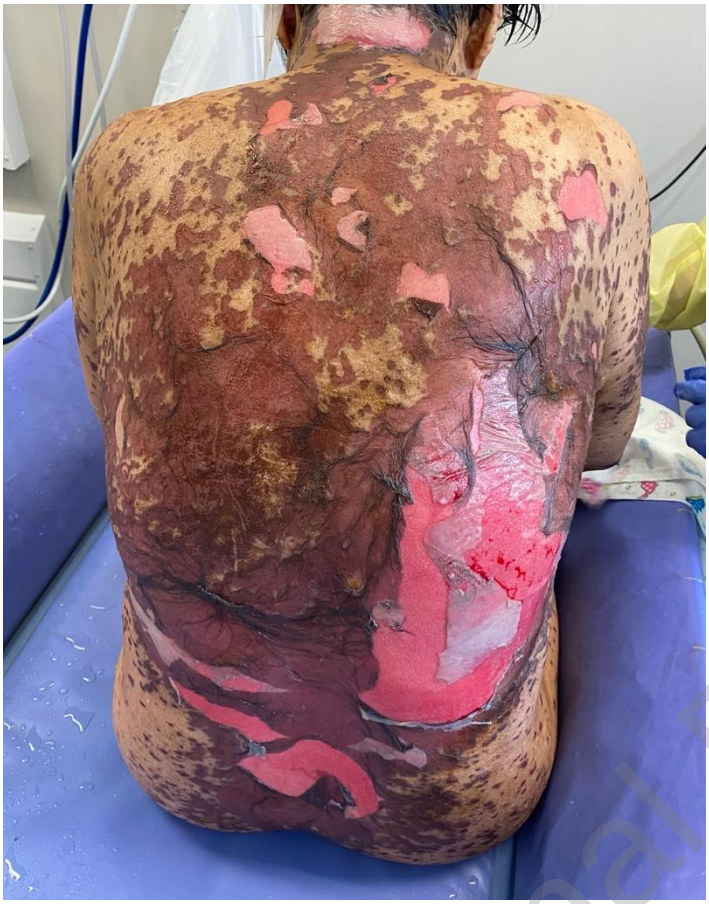
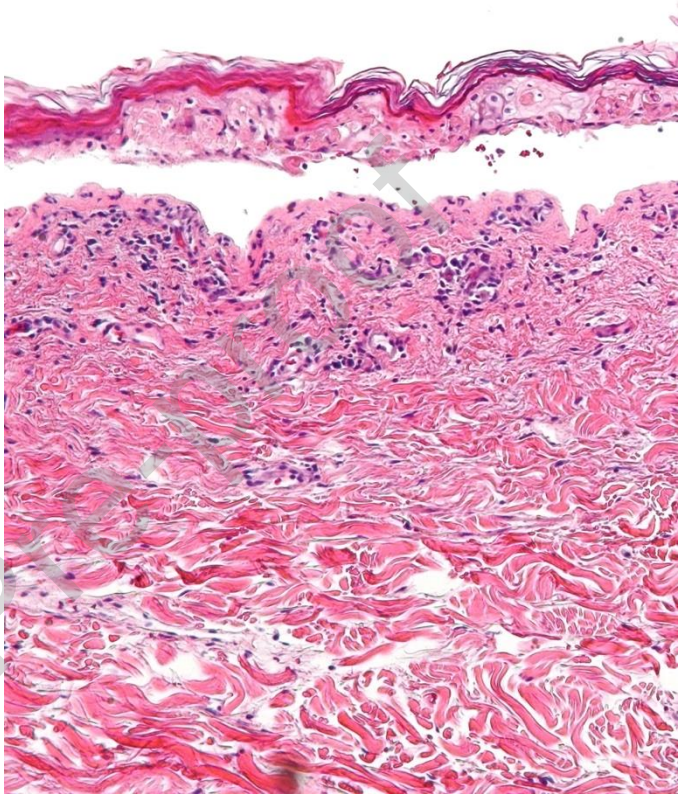




Left: desquamation to back

Right: frozen section demonstrating necrotic keratinocytes, full thickness epidermal necrosis and subepidermal bullae

Figure 2. Cumulative COVID cases

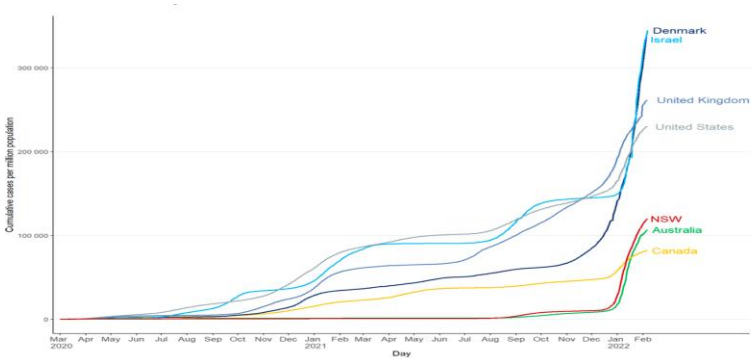


Figure 3. COVID & SJS/TEN cases diagnosed

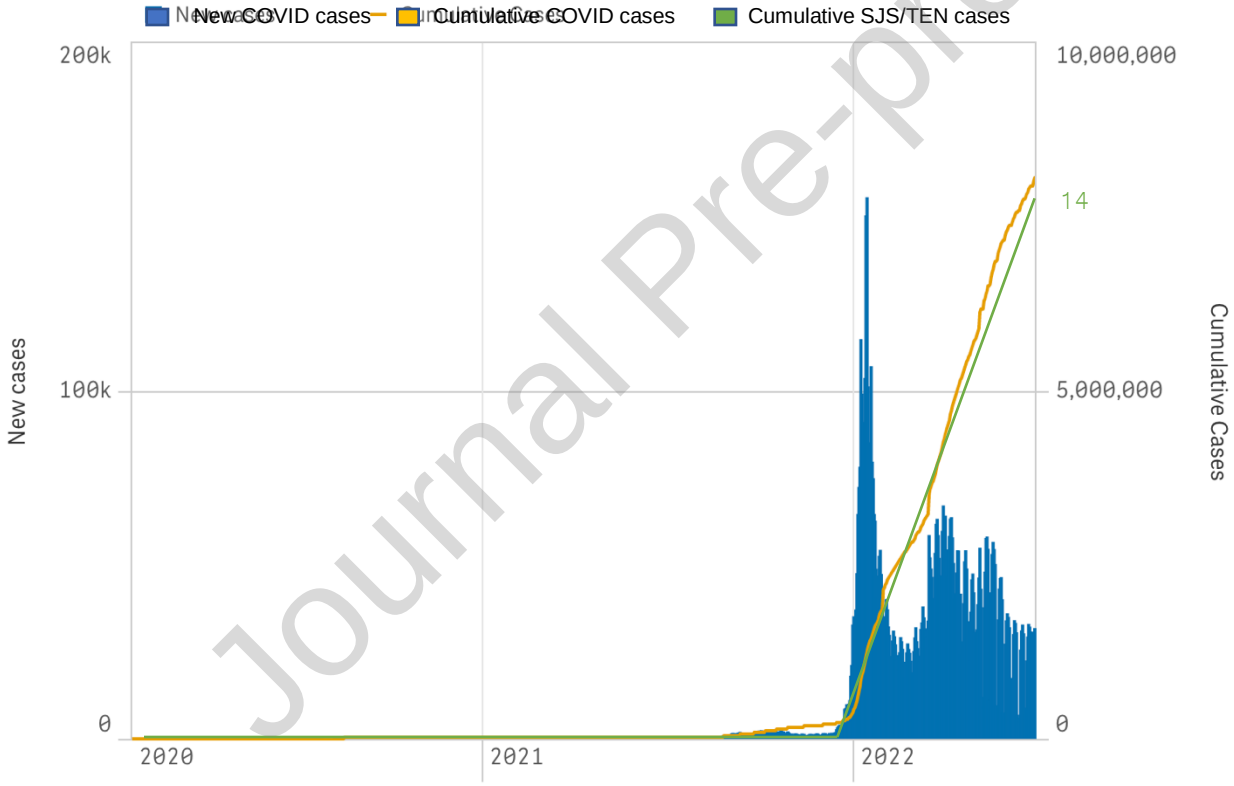
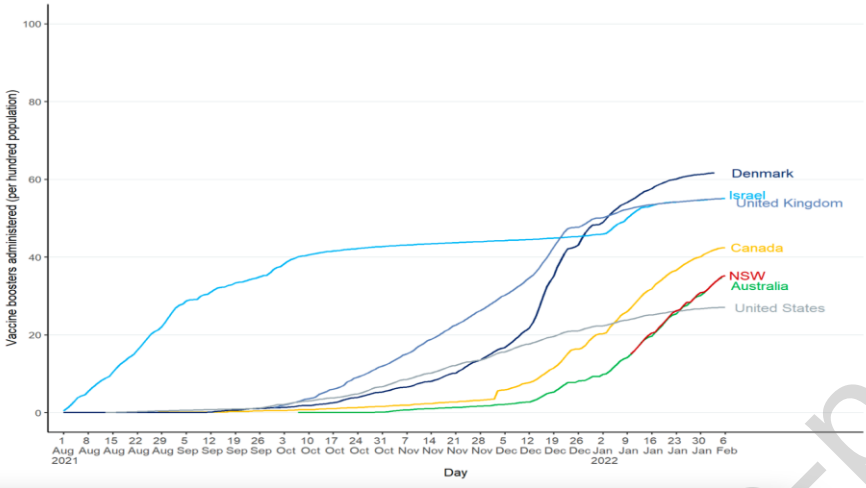


Figure 4. Vaccine booster



Declaration of Competing Interest

None of the authors have any conflicts of interest to declare

Highlights

- There appears to be an association between toxic epidermal necrolysis / Steven's Johnson syndrome and COVID and the vaccine
- Both TEN / SJS and COVID exhibit T cell mediated pathways
- TEN / SJS may be triggered via a virus induced, vaccine induced or threshold lowering pathway