Colistin-associated Stevens-Johnson syndrome and toxic epidermal necrolysis reactions: a retrospective case-non-case pharmacovigilance study

Richard Tang
University of Rhode Island

L. Lopes
University of Rhode Island

Aisling R. Caffrey
University of Rhode Island, aislingcaffrey@uri.edu

Follow this and additional works at: https://digitalcommons.uri.edu/php_facpubs

The University of Rhode Island Faculty have made this article openly available. Please let us know how Open Access to this research benefits you.

Terms of Use
This article is made available under the terms and conditions applicable towards Open Access Policy Articles, as set forth in our Terms of Use.

Citation/Publisher Attribution
Tang, R., Lopes, V. L. & Caffrey, A. R. (2022). Colistin-associated Stevens-Johnson syndrome and toxic epidermal necrolysis reactions: a retrospective case-non-case pharmacovigilance study. Expert Opinion on Drug Safety. Online ahead of print. https://doi.org/10.1080/14740338.2022.2045945
Available at: https://doi.org/10.1080/14740338.2022.2045945

This Article is brought to you for free and open access by the Pharmacy Practice at DigitalCommons@URI. It has been accepted for inclusion in Pharmacy Practice Faculty Publications by an authorized administrator of DigitalCommons@URI. For more information, please contact digitalcommons-group@uri.edu.
Colistin-associated Stevens-Johnson syndrome and toxic epidermal necrolysis reactions: a retrospective case-non-case pharmacovigilance study

The University of Rhode Island Faculty have made this article openly available. Please let us know how Open Access to this research benefits you.

This is a pre-publication author manuscript of the final, published article.

Terms of Use
This article is made available under the terms and conditions applicable towards Open Access Policy Articles, as set forth in our Terms of Use.

This article is available at DigitalCommons@URI: https://digitalcommons.uri.edu/php_facpubs/1728
Colistin-associated Stevens-Johnson syndrome and toxic epidermal necrolysis reactions: A retrospective case-non-case pharmacovigilance study
1. Abstract (count 198)

**Background:** Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening skin reactions. Colistin is a last resort antibiotic with a historically poor safety profile. The association between colistin and SJS/TEN has not been previously quantified.

**Methods:** We identified colistin and SJS/TEN adverse event reports from the Food and Drug Administration Adverse Event Reporting System (FAERS) and calculated effect estimates using OpenEpi.

**Results:** From January 2013 through March 2021, 964 adverse events were reported for colistin. Colistin was listed as a secondary suspect drug in 13 SJS/TEN adverse event reports (1.3%), with a reporting odds ratio of 29.6 (95% confidence interval [CI] 17.1-51.1), and proportional reporting ratio of 29.2 (95% CI 17.0-50.2).

**Limitations:** The limitations that accompany any FAERS study include the voluntary nature of reporting, unclear causal relationship between drug and adverse reaction, underreporting, and wide confidence intervals for rare adverse events like SJS/TEN.

**Conclusion:** Colistin was not the primary suspect drug in any SJS/TEN adverse event reports. We did identify a statistically significant safety signal for SJS/TEN with colistin as a secondary suspect drug. SJS/TEN is not currently included in the colistin product label. This association should be further explored in other pharmacoepidemiologic drug safety studies.
3.1 Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare and life-threatening skin reactions that can occur as an adverse event due to a medication or as a result of an infection. The distinction between the two conditions is that SJS is defined as skin involvement of <10% of total body surface area (TBSA) whereas TEN is defined as >30% of TBSA skin involvement. Skin involvement between the ranges of 10-30% are considered SJS/TEN overlap.[1] For the purpose of this study, all SJS or TEN reactions will be referred to as SJS/TEN. The cause of this reaction revolves around an immune complex mediated type-IV, subtype c, hypersensitivity reaction involving T-cells.[2] This hypersensitivity has been associated with certain classes of medications and possibly certain infections as well. Medications associated with SJS/TEN include, but are not limited to, certain anticonvulsants, certain nonsteroidal anti-inflammatory medications (NSAIDs), allopurinol, and certain antibiotics, including sulfonamides, penicillins, and cephalosporins.[3-5] Non-medications related SJS/TEN reactions have been implicated in literature as well, suggesting that certain infections, such as human immunodeficiency virus (HIV) and Mycoplasma pneumoniae, increase the risk of developing SJS/TEN.[3, 6]

SJS/TEN reactions are life threatening conditions with SJS mortality rates ranging from 5% up to 30%.[7] The disease causes skin detachment and water loss which can lead to acute complications including infections of the skin, pneumonia, and septicemia as well as dehydration, acute malnutrition, and multiple organ failure.[8] In addition to these well-defined acute complications, SJS/TEN is now recognized to cause long term complications even after initial resolution. Long-term sequelae include ocular, mucocutaneous, respiratory, gastrointestinal tract, and psychological complications which ultimately impacts a patient's quality of life. [9, 10]

Colistin is a last resort antibiotic with a historically poor safety profile. The antibiotic belongs to the polymyxin class in which each chemical compound is differentiated by their amino acid sequences and fatty acid side chains. The two primary polymyxins used in clinical practice include polymyxin B and polymyxin E (colistin).[11] Colistin is chiefly effective against strains of gram-negative bacilli such as Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli, and Klebsiella pneumoniae that are resistant to other antibiotics. Off label indications include a nebulized form of colistin for bronchiectasis in both cystic fibrosis (CF) and non-cystic fibrosis patients and hospital-acquired or ventilator-associated pneumonia.[12] Previous pharmacovigilance studies using the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS), as well as other health outcomes
studies, have demonstrated a strong association between colistin and nephrotoxicity especially with increasing cumulative doses of colistin. Colistin, as well as polymyxin B, have both been reintroduced into the antimicrobial armory as multidrug-resistant bacteria are becoming both more prevalent and difficult to treat.[11-14] Due to the known toxicity of colistin and increased risk of SJS/TEN with other antibiotics[1,3-6], we investigated SJS/TEN reporting rates with colistin utilizing FAERS data in this case-non-case study, a study design used specifically to analyze the disproportionality of drug safety events in pharmacovigilance databases.

3.2 Methods
In this retrospective case-non-case study, we analyzed adverse event reports from the FAERS data for the period of January 2013 through March 2021 (analysis date August 2021). Case-non-case studies compares cases of an adverse reaction of interest, in this case SJS/TEN, compared to all other reported reactions, considered non-cases. The FAERS database contains reports of adverse events from the FDA’s post-marketing safety surveillance program and is freely accessible to the public. Ethics approval was not required, as the study utilized a publicly available data source that does not contain any identifiable information. Adverse events are coded under Medical Dictionary for Regulatory Activities (MedDRA) terms, and we included the MedDRA terms Stevens-Johnson syndrome, toxic epidermal necrolysis, and SJS-TEN overlap[15] While manufacturers are mandated by law to report certain adverse events to FAERS, healthcare professionals and patients themselves are able to voluntarily submit adverse event reports to FAERS. [16]

We excluded duplicate reports from the analysis, as well as follow-up reports, and reports missing date, gender, or age. Broad search terms were used to identify reports with the antibiotic of interest, colistin, either as a primary or secondary suspect drug. Multiple forms and brands of colistin were referenced from DrugBank and utilized in our search.[17] The following drug names were included: colistin, colimycine, colistimethate, colomycin, coly-mycin. A secondary analysis evaluating polymyxin B and SJS/TEN reactions was conducted. We compared age, type of reaction, and sex between colistin reports with all other reports, using a t-test, Chi-square test, or Fisher’s Exact test as appropriate. We also assessed time to onset, other adverse events, outcomes, as well as all primary and secondary suspect drugs for colistin and SJS/TEN reports. Reporting odds ratio (ROR), proportional reporting ratio (PRR), and corresponding 95% confidence intervals (CIs) were calculated for SJS/TEN reactions.
with colistin and polymyxin B, as compared with all other medications, using OpenEpi (version 3.01).[18] ROR and PRR confidence intervals which did not contain 1.0 were considered statistically significant.

3.3 Results

Over the study period of January 2013 through March 2021, there were a total of 8,102,577 adverse event reports, and 0.03% (n=3,760) listed SJS/TEN reactions, with 13 of those reports listing colistin as a secondary suspect drug (0.3%; 1 report listed polymyxin B, 0.03%). Patients with SJS/TEN reports listing colistin as a secondary suspect drug were significantly younger than SJS/TEN reports listing other drugs (mean age 38.5 versus 51.7, p=0.04), and more commonly male (84.6% versus 44.1%, p=0.01; Table 1). Most reports were cases of SJS for both colistin (92.3%) and other drugs (61.2%).

For the 13 adverse event reports of SJS/TEN listing colistin, Table 2 describes the primary and secondary suspect drugs from those reports, as well as the time to onset of SJS/TEN, co-occurring adverse events, and clinical outcomes. Colistin was a secondary suspect drug in all reports, and 11 other medications were listed as primary suspect drugs, 6 (54.5%) of which were antibiotics, antivirals, or antifungals. The mean time to onset was 10.6 days (standard deviation 2.6 days; median of 11 days, interquartile range 10-13 days).

Co-occurring adverse events included 8 (61.5%) with other skin problems, 2 (15.4%) with multiple-organ failure, 4 (30.8%) with pancytopenia, and 5 (38.5%) with no other adverse events. None of the report listed nephrotoxicity, impaired renal function, or renal failure. Outcomes for 12 of the 13 cases were recorded, which included 6 (46.2%) patients who died and 6 (46.2%) were listed as life-threatening. The most common other secondary suspect drugs (n=38) included amphotericin B (n=12, 92.4%), ciprofloxacin (n=11, 84.6%), esomeprazole (n=9, 69.2%), fluconazole (n=8, 61.5%), and teicoplanin (n=7, 53.8%).

Colistin had a statistically significant ROR of 29.6 (95% CI 17.1-51.1) and a statistically significant PRR of 29.2 (95% CI 17.0-50.2; Table 3) as a secondary suspect drug for SJS/TEN. There were 89 adverse event reports for polymyxin B with one (1.1%) report of SJS/TEN, resulting in a statistically significant ROR of 24.7 (95% CI 3.4-176.4) and statistically significant PRR of 24.3 (95% CI 3.4-170.7).

3.4 Discussion
The results of our study with recent FAERS data show that colistin was not listed as a primary suspect drug for any SJS/TEN adverse event reports, and therefore this association could not be assessed. When evaluating SJS/TEN adverse event reports where colistin was listed as a secondary suspect drug, reporting rates were almost 30 times higher compared with all other drugs. Existing literature does not mention any association between SJS/TEN and colistin. Further, this reaction is not listed in colistin package inserts. [19-22] A similar association was observed with polymyxin B, a 25 times higher reporting rate than other drugs. However, there was only one report of SJS/TEN and polymyxin B, resulting in a wide confidence interval which limits any conclusions which can be made from this finding.

Though colistin was not the primary suspect drug in any of the 13 SJS/TEN reports, 85% of report had a different primary suspect drug. The secondary suspect drug list consisted of 39 unique drugs, including antibiotics, antivirals, antifungals, proton pump inhibitors or 5-HT3 antagonists. Interestingly, no antiepileptics were listed as primary or secondary suspect drugs among the 13 reports. The most common secondary suspect drugs were amphotericin B (n=12, 92.4%) and ciprofloxacin (n=11, 84.6%), which both include warnings about SJS/TEN reactions in their package inserts [23,24]. Many of the secondary suspect drugs have also been identified as increasing the risk of SJS/TEN using the algorithm of drug causality for epidermal necrolysis (ALDEN). As colistin is used in combination with other drugs associated with SJS/TEN, it is not possible to study the drug safety of colistin alone in observational studies. However, it is important to note the possibility that certain combinations of antibiotics, or antibiotics and antifungals, may increase the risk of SJS/TEN compared with administration of those therapies alone. It will be important for future studies to assess risk of SJS/TEN in the context of combination therapies, relative to the risk of these therapies alone or in other combinations. Such studies would need to assess the incidence of SJS/TEN in patients with serious infections receiving antibiotic regimens which include colistin versus the same/similar regimens without colistin.

Studies have shown with allopurinol and its active metabolite oxipurinol that prior impaired renal function can increase the severity of skin reactions such as SJS/TEN [25]. As nephrotoxicity is a well-recognized drug safety issue with colistin, nephrotoxic effects could impact the risk and severity of SJS/TEN reactions due colistin itself, or due to co-administered drugs which carry the risk of SJS/TEN, including amphotericin B and ciprofloxacin. However, nephrotoxicity, or impaired renal function, were not listed as other adverse events in any of the SJS/TEN adverse event reports, limiting the assessment of these effects.
The Weber effect states that adverse event reporting for a drug is at its highest for the first two years post-marketing approval and begins to drop off thereafter. Interestingly, colistin has been in use clinically for roughly 60 years and still has significant reporting rates for SJS/TEN in the recent FAERS data analyzed. One explanation is that a decline in reporting may occur mainly with clinically mild adverse events, while more serious events are consistently reported year to year. Further, since the Weber effect was first described in 1984, adverse event reporting systems have been modernized, and are now more accessible and streamlined, leading to greater adverse event reporting. Although there is conflicting evidence on the continued validity of the Weber effect, some studies have found that the Weber effect is outdated and may not apply to current day adverse event reporting systems.

Although colistin has been used for around 60 years, its time on the market should not discredit new safety signals. FAERS has been shown to identify previously unknown reactions, even for older medications that have been on the market for decades. Among 233 signals identified from FAERS between 2008 and 2014, most safety signal were associated with newer drugs on the market for less than 5 years (76, 32.6%), however some signals were identified for drugs on the market for 20 years or more (63, 27.0%). One of these signals was mercaptopurine-associated hepatosplenic T-cell lymphoma (HSTCL). Mercaptopurine was in use for 57 years at the time of signal detection and the newly recognized adverse event led to product labeling updates. Similarly, conjugated estrogens were in use for 67 years at the time of signal detection for angioedema, that led to labeling changes. SJS/TEN is a rare condition, with an estimated annual incidence rate of 1 to 5 cases in 1,000,000 individuals, with even higher rates in adults 65 and older which may be due to higher rates of medication use in older populations. The average age for the SJS/TEN reports with colistin as a secondary suspect drug was 38.5 years old. These younger cases may represent a particular patient population at risk of serious infection, such as individuals with CF, who are frequently treated with multiple antibiotics/antifungals and therefore represent an at-risk population if there exists a greater risk of SJS/TEN due to combinations of medications associated with SJS/TEN. FAERS is an effective data source for adverse event signal detection, particularly for rare outcomes and rare exposures, meaning rare adverse events, such as SJS/TEN, and last-line therapies with limited use, such as colistin. Even in very large observational studies (e.g. 10 million individuals or more), there may be too few events to detect an association with any specific medication, especially one that is less commonly used. FAERS, however,
Colistin-Associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Reactions

has been able to detect safety signals for very rare adverse events, for example, mercaptopurine-related HSTCL as
the estimated annual incidence of HSTCL is only 0.3 per million person-years. [29, 30, 32, 38]

The main concerns for colistin associated adverse reactions include nephrotoxicity, neurotoxicity, and
respiratory arrest, most of which are dose dependent.[19-22] A previous FAERS study investigated the most
common antibiotics associated with acute kidney injury (AKI) from 2015 through 2017. They reported that colistin
had the greatest proportion of AKI reports, with a statistically significant ROR of 33.10 (CI 21.24-51.56),
representing nearly 25% of all colistin reports. The study also highlighted the fact that previous studies of AKI
reactions have only included medications with the greatest total number of AKI reports, which ultimately excluded
colistin due to its limited use and corresponding lower number of total reports.[13]

Due to colistin’s well-known adverse effect profile in terms of nephrotoxicity and neurotoxicity, it is
important to consider the possibility that certain adverse effects with colistin may be masked by other drugs
previously shown to be associated with SJS/TEN, such as penicillin, antiepileptics, antipyretics, analgesics, and/or
the infection itself. This may explain why colistin was recorded as a secondary suspect drug in all 13 reports of
SJS/TEN instead of a primary suspect drug. Due to the fact that colistin is often used with other antibiotics,
antivirals, antifungals, and other supportive medications that have been associated with SJS/TEN, the reaction is
more likely to be attributed to those medications with such established risk.

Masking has led to missed signal detection, as evidence from a systemic masking analysis using the
EudraVigilance database of the European Medicines Agency.[42] In this study, ceftriaxone was identified as the
drug with the highest masking effect for anaphylactic shock due to its disproportionate amount of reports. After
removal of ceftriaxone reports, they unmasked an association of fusafungin with anaphylactic shock. This masked
safety signal was detected three years prior to standard signal detection, which eventually led to regulatory action
and market withdrawal. This may explain why colistin was recorded as a secondary suspect drug in all 13 reports of
SJS/TEN instead of a primary suspect drug. Another important aspect of masking to consider is intra-drug masking
or event-competition bias, where disproportionately reported adverse events for a drug can hide other safety
concerns for that same drug. This was observed with statins when reports of commonly reported
rhabdomyolysis/myopathy were removed from a French pharmacovigilance research database (1986 to 2001) and 11
new signals of disproportionate reporting were identified.[43] Similarly, colistin signals may have been masked due
to its disproportionately reported adverse events of nephrotoxicity (n=40, 7.2%).
The limitations of this study relate to the data source and therefore affect all studies utilizing FAERS data. Though these limitations are previously well-described and clearly explained on the FAERS website, [16,44-48] in summary they include (1) the voluntary nature of reporting, (2) hence the reports do not represent estimates of the incidence nor prevalence of adverse reactions with the medications of interest, (3) a low threshold for relatedness of the reaction to the medication (e.g. no requirement that the relationship be clearly causal or that reports utilize ALDEN), (4) missing data, (5) misclassification of medications and/or reactions, (6) underreporting, (7) low adverse report counts for rare events leading to wide confidence intervals, and (8) confounding by co-medications which may or may not (missing data) be included in the report. Patients being treated with colistin are likely also being treated with other antibiotics, as well as supportive care medications such as antipyretics or analgesics which have been linked to causing SJS/TEN, as demonstrated with the 11 primary suspect drugs and 39 secondary suspect drugs.[49,50] As such, these medications may themselves have been responsible for the SJS/TEN reaction, either alone or in combination with colistin or other medications. Due to the low number of SJS/TEN reports with colistin as a secondary suspect drug (n=13), we observed a wide confidence interval. However, even at the low end of the confidence interval, the reporting rates for SJS/TEN with colistin as a secondary suspect drug was nearly 10 times higher than with other medications, indicating a potential safety signal.

3.5 Conclusions

In our pharmacovigilance disproportionality analysis, colistin was not listed as a primary suspect drug for any SJS/TEN adverse event reports, and therefore this association could not be assessed. We did identify a statistically significant safety signal for SJS/TEN with colistin as a secondary suspect drug, where reporting rates were 30 times higher compared with all other medications. SJS/TEN is not currently included in the colistin product label. Evidence of this safety signal should be assessed further in other pharmacoepidemiologic drug safety studies and among other study populations. While the use of a pharmacovigilance database such as FAERS is a reasonable first step in the signal detection process, in this particular case, the database did not have any cases of SJS/TEN listing colistin as a primary suspect drug. Future studies assessing this association will need to utilize large data sources with highly accurate exposure data which allows for either the exclusion or adjustment of concomitant medications which may also increase the risk of SJS/TEN. Should the association be substantiated, provider
education and proper adverse reaction monitoring will be key for early detection to minimize the long-term effects of these serious skin reactions.
Colistin-Associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Reactions

4. References

1. Lerch, M., Mainetti, C., Terziroli Beretta-Piccoli, B., & Harr, T. (2018). Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clinical reviews in allergy & immunology, 54(1), 147–176. https://doi.org/10.1007/s12016-017-8654-z

2. Czarnobilska E, Obtulowicz K, Wsolek K. Reakcja alergiczna typu IV i jej podtypy [Type IV of hypersensitivity and its subtypes]. Przegl Lek. 2007;64(7-8):506-508.

3. Oakley AM, Krishnamurthy K. Stevens Johnson Syndrome (Toxic Epidermal Necrolysis) [Updated 2019 Dec 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459323/

4. Borrelli, E. P., Lee, E. Y., Descoteaux, A. M., Kogut, S. J., & Caffrey, A. R. (2018). Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: An analysis of the US Food and Drug Administration Adverse Event Reporting System. Epilepsia, 59(12), 2318–2324. https://doi.org/10.1111/epi.14591

5. Kardaun SH, Sekula P, Valeyr-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-1080. doi:10.1111/bjd.12501

6. Kim, H. I., Kim, S. W., Park, G. Y., Kwon, E. G., Kim, H. H., Jeong, J. Y., Chang, H. H., Lee, J. M., & Kim, N. S. (2012). Causes and treatment outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in 82 adult patients. The Korean journal of internal medicine, 27(2), 203–210. https://doi.org/10.3904/kjim.2012.27.2.203

7. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults. J Invest Dermatol. 2016 Jul;136(7):1387-1397. doi: 10.1016/j.jid.2016.03.023. Epub 2016 Mar 30. PubMed PMID: 27039263.

8. Stevens-Johnson syndrome/toxic epidermal necrolysis - Genetics Home Reference - NIH. (2020, May 12). Retrieved May 18, 2020, from https://ghr.nlm.nih.gov/condition/stevens-johnson-syndrome-toxic-epidermal-necrolysis#definition

9. Lee, H. Y., Walsh, S. A., & Creamer, D. (2017). Long-term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): the spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multidisciplinary follow-up. The British journal of dermatology, 177(4), 924–935. https://doi.org/10.1111/bjd.15360
10. Yang, C. W., Cho, Y. T., Chen, K. L., Chen, Y. C., Song, H. L., & Chu, C. Y. (2016). Long-term Sequelae of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. *Acta dermato-venereologica*, 96(4), 525–529. https://doi.org/10.2340/00015555-2295

11. Matthew E. Falagas, Sofia K. Kasiakou, Louis D. Saravolatz, Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections, *Clinical Infectious Diseases*, Volume 40, Issue 9, 1 May 2005, Pages 1333–1341, https://doi.org/10.1086/429323

12. Colistimethate. In: Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2016 [updated 18 May 2020; cited 19 May 2020]. Available from: http://online.lexi.com. Subscription required to view.

13. Patek, T. M., Teng, C., Kennedy, K. E., Alvarez, C. A., & Frei, C. R. (2019). Comparing Acute Kidney Injury Reports Among Antibiotics: A Pharmacovigilance Study of the FDA Adverse Event Reporting System (FAERS). *Drug Safety*, 43(1), 17–22. doi: 10.1007/s40264-019-00873-8

14. Spapen, H., Jacobs, R., Van Gorp, V., Troubleyn, J., & Honoré, P. M. (2011). Renal and neurological side effects of colistin in critically ill patients. *Annals of intensive care*, 1(1), 14. https://doi.org/10.1186/2110-5820-1-14

15. **Center for Drug Evaluation and Research. (2018, June 04). Questions and Answers on FDA’s Adverse Event Reporting System (FAERS). Retrieved June 11, 2020, from https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers**

16. Chedid, V., Vijayvargiya, P., & Camilleri, M. (2018). Advantages and Limitations of the Federal Adverse Events Reporting System in Assessing Adverse Event Reporting for Eluxadoline. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, 16(3), 336–338. https://doi.org/10.1016/j.cgh.2017.11.025

17. Colistin. (2020, March 15). Retrieved March 16, 2020, from https://www.drugbank.ca/drugs/DB00803

18. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2020/03/19.

19. National Library of Medicine (U.S.). (2005). *DailyMed*. Bethesda, MD: U.S. National Library of Medicine, National Institutes of Health, Health & Human Services.
20. **Colistin [package insert]. Toronto, ON Canada: Fresenius Kabi Canada Ltd.; 2017.

The reference demonstrates that the package insert for colistin does not contain information for SJS/TEN.

21. Coly-Mycin M Parenteral [package insert]. Rochester, MI: Parkedale Pharmaceuticals Inc.; 2006.

22. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: 05/28/2020).

23. Ciprofloxacin [Package insert]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc; 2016.

24. Amphotericin B [Package insert]. Big Flats, NY: X-Gen Pharmaceuticals Inc; 2009.

25. Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis*. 2015;74(12):2157-2164. doi:10.1136/annrheumdis-2014-205577

26. Weber J. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. *Adv Inflamm Res*. 1984;6:1–7.

27. Hoffman, K. B., Dimbil, M., Erdman, C. B., Tatonetti, N. P., & Overstreet, B. M. (2014). The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug safety*, 37(4), 283–294. https://doi.org/10.1007/s40264-014-0150-2

28. Chhabra, P., Chen, X., & Weiss, S. R. (2013). Adverse event reporting patterns of newly approved drugs in the USA in 2006: an analysis of FDA Adverse Event Reporting System data. *Drug safety*, 36(11), 1117–1123. https://doi.org/10.1007/s40264-013-0115-x

29. Hartnell, N. R., & Wilson, J. P. (2004). Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy*, 24(6), 743–749. https://doi.org/10.1592/phco.24.8.743.36068

30. Arora A, Jalali RK, Vohora D. Relevance of the Weber effect in contemporary pharmacovigilance of oncology drugs. *Ther Clin Risk Manag*, 2017;13:1195-1203 https://doi.org/10.2147/TCRM.S137144

31. **Fukazawa, C, Hinomura, Y, Kaneko, M, Narukawa, M. Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA. *Pharmacoepidemiol Drug Saf*. 2018; 27: 1402–1408. https://doi.org/10.1002/pds.4672
The article supports the possibility of late signal detections for well-established drugs that have been on the market for an extended period of time.

32. *Drug Safety communication. Available at http://wayback.archive-it.org/7993/20171115033743/https://www.fda.gov/Drugs/DrugSafety/ucm250913.htm. Accessed August 7, 2018.

This reference demonstrates the strengths of FAERs to detect safety signals for rare adverse events.

33. Mercaptopurine (Purinethol) Labeling approved May 27, 2011 (PDF - 60KB). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009053s032lbl.pdf. Accessed August 7, 2018.

34. Conjugated estrogens (Premarin) labelling approved October 28, 2011 (PDF - 310KB). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/004782s162s164s167lb.pdf. Accessed August 7, 2018.

35. Orphan Drug Act of 1983. Pub L. No. 97–414, 96 Stat. 2049.

36. FAQs About Rare Diseases. (2017, November 30). Retrieved July 21, 2020, from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases

37. Rare diseases. (2020, June 24). Retrieved July 21, 2020, from https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/rare-diseases_en

38. White, K. D., Abe, R., Arden-Jones, M., Beachkofsky, T., Bouchard, C., Carleton, B., Chodosh, J., Cibotti, R., Davis, R., Denny, J. C., Doduk-Gad, R. P., Ergen, E. N., Goldman, J. L., Holmes, J. H., 4th, Hung, S. I., Lacouture, M. E., Lehloenya, R. J., Mallal, S., Manolio, T. A., Micheletti, R. G., … Phillips, E. J. (2018). SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. *The journal of allergy and clinical immunology. In practice*, 6(1), 38–69. https://doi.org/10.1016/j.jaip.2017.11.023

39. Chan, H. L., Stern, R. S., Arndt, K. A., Langlois, J., Jick, S. S., Jick, H., & Walker, A. M. (1990). The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Archives of dermatology, 126*(1), 43–47.

40. Roujeau, J. C., Guillaume, J. C., Fabre, J. P., Penso, D., Fléchet, M. L., & Girre, J. P. (1990). Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Archives of dermatology, 126*(1), 37–42. https://doi.org/10.1001/archderm.126.1.37
41. Montgomery, M., van Santen, M. M., Biemond, B. J., Diamond, R. H., & Pals, S. T. (2015). Hepatosplenic T-Cell Lymphoma: A Population-Based Study Assessing Incidence and Association With Immune-Mediated Disease. *Gastroenterology & hepatology, 11*(3), 160–163.

42. *Hauben, M., and Maignen, F. (2017) Does serious consequential masking exist? An update. *Pharmacoepidemiol Drug Saf, 26*: 727–729. doi: 10.1002/pds.4209.

This study demonstrated the significance of masking for serious adverse events in signal detection.

43. Salvo, F., Leborgne, F., Thiessard, F., Moore, N., Bégaud, B., & Pariente, A. (2013). A potential event-competition bias in safety signal detection: results from a spontaneous reporting research database in France. *Drug safety, 36*(7), 565–572. https://doi.org/10.1007/s40264-013-0063-5

44. Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf. 2001;10(5):407-10.

45. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *J Gen Intern Med. 2003;18*(1):57-60.

46. Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy. 2004;24*(6):743-9.

47. Rothman KJ, Lanes S, Sack ST. Reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(5):519-23.

48. U.S. Food & Drug Administration. Questions and answers on FDA's adverse event reporting system (FAERS). U.S. Department of Health and Human Services; 2018.

49. Abdulah, R., Suwandiman, T. F., Handayani, N., Destiani, D. P., Suwantika, A. A., Barliana, M. I., & Lestari, K. (2017). Incidence, causative drugs, and economic consequences of drug-induced SJS, TEN, and SJS-TEN overlap and potential drug-drug interactions during treatment: a retrospective analysis at an Indonesian referral hospital. *Therapeutics and clinical risk management, 13*, 919–925. https://doi.org/10.2147/TCRM.S142226

50. Nakamura, R., Kaniwa, N., Ueta, M., Sotozono, C., Sugiyama, E., Maekawa, K., Yagami, A., Matsukura, S., Ikezawa, Z., Matsunaga, K., Tokunaga, K., Aihara, M., Kinoshita, S., & Saito, Y. (2014). HLA association with antipyretic analgesics-induced Stevens-Johnson Syndrome / toxic epidermal necrolysis with severe ocular surface complications in japanese patients. *Clinical and Translational Allergy, 4*(Suppl 3), P89. https://doi.org/10.1186/2045-7022-4-S3-P89