Corticosteroid intervention on the outcomes of adolescent and young adult patients (aged 15-30) with e-cigarette and vaping product use associated lung injury (EVALI), a systematic review.

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Abstract

Background: Worldwide, vaping prevalence rates for youth are on the rise. Electronic cigarette and vaping product use associated lung injury (EVALI), is associated with increased use and requires effective treatment such as corticosteroid therapy.

Objective To examine literature for analysis of corticosteroid treatment, including clinical course specifics and effect on the improvement of EVALI patient outcomes (aged 15-30).

Methods Adhering to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines, confirmed or probable cases of EVALI in patients aged 15-30 were identified using PubMed, Scopus, Ovid, Web of Science and The Cochrane Library databases. Studies included were published in English, with e-cigarette exposure 90 days before symptom onset and assessed at least two outcomes on patient follow up. Studies excluded were patients outside of the defined age range or with comorbidities. Quality and risk of bias assessment was performed on the final 8 studies, all of which were published in 2020.

Results As presented across all studies in the current review, corticosteroid (CS) treatment for adolescent and young adult EVALI patients results in improved patient outcomes, both in documented patient notes and in improved Pulmonary Function Test (PFT) capacity, association with shorter hospitalization durations and less required oxygen support on discharge.

Conclusion Intravenous (IV) or oral corticosteroids, including prednisolone and methylprednisolone were prescribed in majority of cases with many cases noting improvement of outcomes due to clinical intervention. Specifics of the courses, including duration, dosage and length of taper varied significantly between cases and studies. Improvement of outcomes as measured through PFT following CS intervention was noted, but deterioration in the outpatient setting also occurred.

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1. Introduction

Vaping and electronic cigarette exposure seriously damages developing lungs. As of January 7 2020, 2602 cases of electronic cigarette and vaping product use associated lung injury (EVALI), have been reported to the Centres for Disease Control and Prevention (CDC), from all 50 states in the United States of America (USA).[1] The main demographic of these patients are adolescents and young adults, with 62% being between 18-34 years old[2]

EVALI, one of notable adverse effects associated with e-cigarette use, is characterized by the CDC as bronchitis and pneumonitis due to chemicals, fumes, or the

inhalation of oils, pulmonary eosinophilia and acute respiratory distress syndrome (ARDS).[4] Confirmed cases of EVALI, as defined by the CDC in 2019, have the following criteria: "Vaping" or "dabbing" within 90 days prior to symptoms, pulmonary opacities on chest radiograph or ground-glass opacities (GGO) on chest computerized tomography (CT) scan, negative infectious and immunologic panel, exclusion of alternative diagnoses.[5]

As cases of EVALI mount in the literature in the form of case reports and case series, so does evidence of clinical intervention. In October 2019, the CDC released interim guidance for possible treatment of EVALI using corticosteroids to diminish inflammation associated with the condition.[6] Corticosteroids (CS) have also been used in the treatment of ARDS, with varying results and successes.[7] It is therefore important to investigate whether CS therapy can improve the outcomes of EVALI patients. The outcomes to be examined for improvement with CS therapy in this review include; duration of hospitalization, Pulmonary Function Testing (PFT) results, and the level of oxygen support required on discharge. Clinical improvement in current research has been measured through spirometry at discharge and short term follow up of patients, where abnormalities in the PFT results, including airway obstruction, or restriction and reduced capacity for diffusion of carbon monoxide have been observed.[8]

Due to the recent timeline of the outbreak, clinical trials and cohort studies are lacking to definitively support this clinical intervention, and little information about dosage, preferred drug type, mechanism of administration or time of administration during hospitalization of CS therapy has been recorded. This review has therefore compiled all relevant literature to examine whether corticosteroid intervention does improve the outcomes of adolescent patients and young adult patients (aged 15-30) with documented or probable EVALI.

2. Materials and Methods

Adhering to the PRISMA guidelines, the review aimed to collect all relevant clinical trials, systematic reviews, cohort studies, and case series.

To identify published studies, searches were conducted on Cochrane, PubMed, Web of Science, Scopus, and Ovid databases. A time frame was not set to not miss the earliest publications. The terms used were "electronic cigarette", "e-cigarette", "vaping" , "acute lung injury", "EVALI", "VAPI", "respiratory effect", "adolescent", "teenager", "youth", "young adult", "steroid", "corticosteroid", "glucocorticoid", "prednisone", "prednisolone", "outcome", "hospitalization", "intervention", "treatment" and "therapy". Additional case series were identified manually in the references of other case reports or case series. Reports published by the CDC in relation to the outbreak of EVALI and youth in the USA were also searched.

2.1 Inclusion and Exclusion Criteria

Screening: Initial screening was of titles and abstracts, excluding studies that were done on animals or were related to the regulation or policy sector of e-cigarette management.

For inclusion, studies considered were published in English and consisted of clinical trials, systematic reviews, reports, cohort studies and case series. For a high-quality analysis, case reports were not included in this review. Additionally, patients within the studies had to fall between 15 and 30 years of age with exposure to e-cigarette or vaping products 90 days prior to symptom onset and no existing comorbidities.

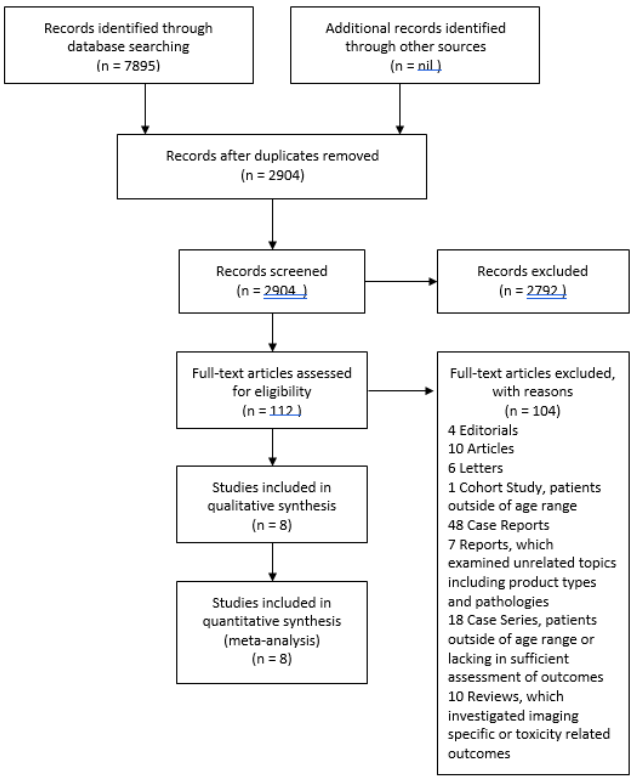
Eligibility: Studies were subsequently examined, and each assessed for their quality of clinical presentation, information abundance and details given on the outcomes and treatments of each respective patient.

2.2 Search Results

As of June 18 2020, search results yielded 7895 studies including case reports, CDC reports, cohort studies, letters, editorials and systematic reviews. Following the aforementioned inclusion criteria, the final list consisted of 8 studies: 1 cohort study and 7 case series (**Figure 1**). A large portion of records were excluded upon screening as much of the literature examined other, unrelated, consequences of e-cigarette usage; including, but not limited to regulatory processes, demographical studies, and chemical analysis of compounds.

The lack of more rigorous studies suggests there is scope for more research and highlights the importance of this review in mapping the current use of corticosteroids in clinical intervention.

Figure 1. PRISMA Flowchart of Included Studies



2.3 Quality and Risk of Bias Assessment

Quality of the final eight studies was assessed using tools from the Joanna Briggs Institute (JBI) for case series and the Newcastle-Ottawa Scale for cohort studies. JBI was selected for their extensive use and acceptance in the scientific community, as well as their peer review process. The Newcastle-Ottawa Scale was selected because of the definitive point system and specific application to cohort studies. Risk of bias was assessed by ROBINS-1 tool because of frequent citations across the literature and ease of usage.

2.4 Statistical Analysis

Analysis of the selected studies resulted in 157 patients with a median age of 17.7, ranging from 15-29. Overall, 73% of patients were males, 27% were female. In studies where description of participants by ethnicity was included, 78-100% of cases were Caucasian. [9] [10] In one study, 46% of participants were Hispanic.[11]

3. Results

3.1 Corticosteroid Clinical Course

Studies included in this review treated 43 to 100% of adolescent patients presenting with EVALI and treated with some type of CS therapy. Doses, methods of administration and duration of treatment ranged between the studies and are presented in **Table 1.**

IV methylprednisolone administration was commonly used amongst the studies, with 4/8 studies citing it's use for systemic treatment with a rate of administration between 125 mg/ 6 hours to 1g / day. [9] [12] In the study conducted by Layden et al, of the 84% of patients treated with CS, 81% received IV administration and the other 19% received oral treatment.[10] Prednisolone was administered orally at 60mg per day in 3/8 studies, and one at 40mg per day.[12]

The duration of CS treatment varied between studies, ranging from <7 - >21 days of therapy. Layden et al state that all but 5 courses of corticosteroids lasted < 7 days while Carroll et al classified their courses into 3 treatments based on duration; short (8 days), intermediate (14 days) and extended (more than 21 days). [9] [10]

The majority of the courses of CS across all studies were followed with a subsequent taper, which ranged from 5 days to 6 weeks, with some studies failing to report the exact taper duration prescribed. Other methods of CS administration included pulse dosing in 7/11 patients in the study completed by Rao et all. [10]

Early administration of corticosteroids was associated with decreased duration of hospitalization in data presented by Layden et al, and through early recognition of EVALI, clinicians in the study conducted by Carroll et al were able to reduce the time from hospital admission to administration of corticosteroids from 6.6 days to 1.5 days. [9] [10]

Table 1. Clinical Course of Corticosteroid Treatment

			Therapy		
Study	Design Type	Number of Patients Treated with Corticosteroids (%)	Systemic (number of patients)	Oral (number of patients)	Mean Course Duration (days)
Carroll, 2020	Cohort Study	15 (100)	13	2	18.8
Chidambaram, 2020	Case Series	10 (91)	-	-	-
Choe, 2020	Case Series	3 (75)	1	2	16
Corcoran, 2020	Case Series	3 (43)	2	1	9.3
Layden, 2020	Case Series	82 (84)	66	16	94% of courses were greater than 7 days
Messina, 2020	Case Series	5 (83)	-	-	10.2
Rao, 2020	Case Series	12 (92)	11	1	-
Silverman, 2020	Case Series	3 (100)	-	-	7.6 + unknown steroid taper

3.2 Corticosteroid Treatment on Patient Improvement

Documented improvement in EVALI patients from CS therapy was observed in all studies, with 6/8 noting improvement or resolution in the patient notes of all cases following treatment. [11 12 13] In the case series presented by Messina et al, improvement of 11/12 patients were noted within 24 hours. [14] This data is presented in **Table 2**.

Other studies noted partial improvement, but incomplete symptom resolution in EVALI patients, with Carroll et al reporting only 5/11 cases were completely resolved at discharge. [9] Layden et al report documented evidence of improvement in only 51% of the patient notes. [10]

Oxygen support at discharge varied amongst the studies, with some able to discharge all patients on room air, and others requiring supplemental oxygen support following treatment in 17-31% of patients. [11 12 13 15]

While patient improvement with CS treatment was consistently reported amongst the studies, complications, including the development of a pneumomediastinum in one patient and 2 deaths were noted in 2 of the studies. [10 15]

3.3 Corticosteroid Treatment on PFT Results

Abnormal spirometry and decreased diffusion capacity of the lung for carbon monoxide (DLCO) as investigated by PFT has been well-documented in the literature on EVALI patients. The studies included in this review are no different in their reports, with 6/8 studies investigating spirometry measures including; forced expiratory volume for one second (FEV1), forced vital capacity (FVC) DLCO, 6-minute walk tests (6MWT) and pulmonary obstruction or restriction. In the case series presented by Rao et al, all patients had improved PFT outcomes after the administration of corticosteroids, ranging between 9-35% on FEV1, FVC and DLCO. [12] Chidambaram et al noted that the FEV1 capacity increased from 88% to 99% while patients were in hospital. [16]

Yet the studies in this review were also consistent in reporting the deterioration of PFT upon the patients' transition to outpatient care. In the cohort study completed by Carroll et al, 5/11 patients needed to be treated with inhaled corticosteroids (ICS) in the outpatient setting for residual abnormalities, all of which experienced reduced capacity on follow up. [9] A patient in the case series presented by Choe et al presented with continued hoarseness of voice at follow up, while Rao et al noted 2/13 patients whose PFT remained abnormal after steroid treatment. [12 13] The differences between PFT results following CS therapy in both the inpatient and outpatient settings for the adolescent EVALI patients included in this review are summarized in **Table 2**.

3.4 Corticosteroid Treatment on Duration of Hospitalization

The duration of hospitalization of adolescent and young adult EVALI patients included in this review ranged from 2- 31 days, with many studies reporting admission to their ICU or PICU departments. The median stay across all studies was 8.1 days.

Data from Corcoran et al on the difference duration of hospitalization between those patients treated with corticosteroids and those without was analysed statistically using Comprehensive Meta-Analysis software, and can be found in the supplementary appendix (**Appendix 1**). The Hedge's g between the corticosteroid and non-corticosteroid group was found to be somewhere between a small and medium effect at 0.297.

Table 2. Comparisons in Patient Spirometry and Improvement

Study	Spirometry			Patient Improvement	
	Measure	Inpatient	Outpatient	Improved	Oxygen Support
Carroll, 2020	Obstructive Restrictive Mixed Decreased DLCO Abnormal 6-minute walk test	2/11 4/11 0/11 3/5 2/4	5/11 1/11 1/11 4/9 1/7	5/11	14/15 discharged on room air
Chidambaram, 2020	Decreased DLCO Mean FEV1 Mean DLCO	3/6 81 78%	 99 74.8%		
Choe, 2020	Decreased DLCO		1/4	4/4	4/4 discharged on room air
Corcoran, 2020	Non-obstructive Median Predicted FEV-1 Decreased DLCO	6/7 105%	 3/7		7/7 discharged on room air
Layden, 2020	Oxygen Saturation	33% of patients between 89-94% 25% of patients > 89%		40/78 *in patient notes	
Messina, 2020	Obstructive Restrictive Decreased DLCO	1/4 2/4 2/4			5/6 discharged on room air
Silverman, 2020				3/3	1/3 discharged with supplemental oxygen
Rao, 2020	Abnormal 6MWT Obstructive FEV1	 66.8%	4/8 2/13 89.6%	11/12 *within first 24 hours	31% discharged with supplemental oxygen

3.5 Additional Therapies for EVALI

While not within the scope of the review, other clinical interventions in addition to CS were mentioned in the studies included in this review, including; supplementary oxygen, n-

acetyl cysteine (NAC), prone positioning on VV-ECMO, and numerous antibiotic therapies. Messina et al report that 69% of patients were given antibiotics prior to corticosteroid intervention, and no improvement was noted with this therapy alone. [10 13 15]

Nonetheless, in cases where patients needed multiple therapies, including intubation, mechanical ventilation or supportive oxygen to correct the most common EVALI symptom of hypoxemia, it was CS therapy that resulted in the most improvement. [13]

4. Discussion

4.1 Improvement in Patient Outcomes Due to Corticosteroid Therapy

As presented across all studies in the current review, CS treatment for adolescent and young adult EVALI patients was associated with improved patient outcomes, both in documented patient notes and in improved PFT capacity, association with shorter hospitalization durations and less required oxygen support on discharge. These findings were supported in all studies, and Choe et al state that bwith early administration of CS or other anti-inflammatory therapies, it may be possible to prevent EVALI progression into complete respiratory failure. [13] These findings, however, are subject to various limitations and biases that will be discussed in Section 4.3.

4.2 Similarities and Differences of Corticosteroid Therapy for EVALI Patients

The administration of CS is also important to discuss, as the length of taper and use of pulse dosing are clinically relevant to the clinical improvement of patients. Pulse dosing, or the administration of high doses of methylprednisolone intravenously in an intermittent manner, as reported in the case series published by Rao et al, has been attributed in some studies to enhance the therapeutic effect and diminish side effects. [17] The use of the steroid taper is to the same effect, to prevent rebounds and reduce symptoms of withdrawal. These methods were reported consistently amongst studies included in this review.

However, some studies of inhaled corticosteroid treatment for acute asthmatics found that tapering of steroid therapy is unnecessary, as no significant changes in peak expiratory flow rate (PEFR) were noticed.[18] Discrepancies in the effectiveness of the steroid taper as well as the recommended taper length are evidently existent between conditions and treatment regimes, and as such, should be investigated with specific focus on EVALI patients.

As with any therapy considered for the treatment of a condition, it is also important to consider the impacts of said therapy on the population in question. Corticosteroids, oral, inhaled and intravenous, are long standing drugs for the treatment of asthma, allergies and many other inflammatory conditions, all of which affect young people. Most recently, the Recovery Trial, a National Clinical Trial of Randomized Evaluation of Covid-19 Therapy has been testing low dose dexamethasone on children for treatment of the SARS-Cov-2 virus. [21]

However adverse events attributed to prolonged CS use have been cited in the literature, including infection, venous thromboembolism, avascular necrosis, osteoporosis, diabetes mellitus and Cushing's Syndrome. [19] Adverse Psychological Side Effects (APSE) have also been reported in the literature at any time during treatment, including withdrawal, though clear risk factors or indications of incidence and prevalence do not currently exist.[20]

4.3 Limitations

The novelty of the EVALI outbreak, especially amongst adolescents and young adults, suggests the importance of continued research on the subject, but also creates limitations in the current review.

With no standard set of PFTs, differing clinical courses of CS, and the loss of patients at follow up in pulmonary clinics makes a standard comparison of these studies difficult to complete. The possibility of further exposure to e-cigarette usage could also be explanatory for the diminished PFTs of EVALI patients in the outpatient setting.

These limitations affect the most notable findings of the effect of CS therapy on patients included in this review including; 1) reduced hospitalization duration for patients treated with CS, 2) improved effectiveness with early administration of CS and 3) prolonged dose of CS in improved outcomes.

In Section 3.1, a link between earlier admission of CS therapy and duration of hospitalization was acknowledged in the study completed by Layden et al. [10] However, it is important to consider the possible effect of the "Immortal Time Bias" noted by Suissa in the study of pharmacoepidemiology, where the outcome under study could not occur due to the exposure definition. [16]

In Section 3.4, analysis of the case series completed by Corcoran et al, [11] demonstrated a small to medium effect of corticosteroids in reducing the length of hospitalization. This however, can be confounded by factors including; differing practices between hospitals, patient specifics and more.

Finally, when examining the length of course of corticosteroid treatment, as seen in Section 1, the majority of studies cited the use of CS for at least 7 days, with many favouring a prolonged course with a longer taper upon discharge. One patient in the cohort study presented by Carroll et al that only received a short course resulted in a relapse, however the circumstances with which this occurred were not reported. It is possible that subsequent exposure to e-cigarette and vaping products as well as their harmful vapours, oils and other inhalants took place following treatment.

4.4 Recommendations

In order to counteract these limitations, and more effectively approach the growing EVALI problem, developments must be made in the research, clinical and policy related domains that surround the issue.

More comprehensive, high quality studies must be completed to understand the effect of CS therapy on EVALI patients. A better understanding of what therapies are being used, and to what effect, will help drive best practices in the clinical setting. While steps are already being taken to this effect by the development of a diagnostic tool by Kalinisky et al, further research would drive more comprehensive and complete diagnoses, treatments and follow-ups post-discharge. [23] As well, tangible evidence from reliable and legitimate sources will help force policy makers to act on adolescent and young adult access to e-cigarettes and vaping products. By reducing access, raising awareness, and supporting the efforts with strong research and effective therapies, the EVALI outbreak could be controlled.

4.5 SARS-Cov-2 Statement

As with many 2020 publications, the current review was completed during the outbreak of the novel SARS-Cov-2 virus. Many cases of EVALI presenting to hospital were initially diagnosed as potential positives for the virus, due to the similarity of symptoms. This suggests the importance of a full and complete history of patients with suspected EVALI in order to assess e-cigarette exposure. Other publications suggest that vaping exposure may make patients less able to mount a response against the virus due to impaired lung function. [21] While not directly in the scope of the study, acknowledgment of the climate within the

health sector at the time of this review and possible intersections between EVALI and SARS-Cov-2 is necessary.

It is also important to acknowledge that while this research was not heavily impacted by the situation of the pandemic, health care professionals and front line workers were actively involved in the treatment of patients, maintenance of hospitals numerous additional tasks during the global state of uncertainty and crisis.

5. Conclusion

The current review aimed to investigate the effect of corticosteroid therapy on improving the outcomes of adolescent patients with documented or probable EVALI. The most common drugs, length of courses, and duration of tapers as well as implication on PFTs and hospitalization duration from the 8 studies included in this review were demonstrated.

Physicians should be aware of the potential adverse effects associated with prolonged corticosteroid use and consult with guidance from the CDC as well as up to date research for best practices on the treatment of EVALI, including corticosteroid therapy. Regulatory organizations such as the CDC, FDA and the WHO should be in constant effort to protect adolescents, young adults and all others from the harmful effects of EVALI through public health and regulatory action, while making efforts to investigate the most effective therapies and protocol for the treatment of the condition.

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7. Appendix 1

Data extracted from the case series presented from Corcoran et al, and computed in Comprehensive Meta-Analysis Software. Hedge's g denotes the effect size, or how much the experimental group differs from the control group. The value of -0.297 as shown in this analysis is between small (0.2) and medium (0.5) effect.

Corticosteroid Mean Hospitalization Duration	Corticosteroid Std-Deviation	Corticosteroid Sample Size	Control Mean Hospitalization Duration	Control Std-Deviation	Control Sample Size
7.000	2.640	3	7.750	1.707	4

Std Diff in Means	Std Err	Hedge's g	Std Err	Difference in Means	Std Err
-0.352	0.770	-0.297	0.648	-0.750	1.627