# COPD and Herpes Zoster: Risk and Immunization

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**Abstract**

Varicella Zoster is a neurotropic virus which leads to acute varicella or it may lay dormant in the spinal root ganglion. Reactivation of varicella zoster causes Herpes Zoster (HZ) and occurs commonly in immunosuppressed conditions like COPD. Severity of Herpes Zoster is also higher among those with comorbidities like COPD. Even among COPD patients, the severity of HZ is said to be higher among those using oral corticosteroids than those using inhaled steroids due to greater immunosuppressive effect. It has also been found that incidence rate of COPD exacerbations, transient ischemic attack and stroke are higher among COPD patients with HZ compared to those without HZ. Herpes zoster vaccinations prevent reactivation of latent HZ and reduce the associated complications. Live attenuated and recombinant vaccines are available for vaccination among which recombinant vaccine is found to be more effective. The cost burden due to HZ among COPD patients was also higher compared to those without HZ. Childhood varicella vaccination is cost effective, however cost effectiveness of adolescent vaccination is unclear.

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## Keywords

COPD; herpes zoster; steroids; vaccine; varicella

## Abstract

Varicella Zoster is a neurotropic virus which leads to acute varicella or it may lay dormant in the spinal root ganglion. Reactivation of varicella zoster causes Herpes Zoster (HZ) and occurs commonly in immunosuppressed conditions like COPD. Severity of Herpes Zoster is also higher among those with comorbidities like COPD. Even among COPD patients, the severity of HZ is said to be higher among those using oral corticosteroids than those using inhaled steroids due to greater immunosuppressive effect.

It has also been found that incidence rate of COPD exacerbations, transient ischemic attack and stroke are higher among COPD patients with HZ compared to those without HZ.

Herpes zoster vaccinations prevent reactivation of latent HZ and reduce the associated complications. Live attenuated and recombinant vaccines are available for vaccination among which recombinant vaccine is found to be more effective.

The cost burden due to HZ among COPD patients was also higher compared to those without HZ. Childhood varicella vaccination is cost effective, however cost effectiveness of adolescent vaccination is unclear.

# 1. Introduction

Herpes zoster (HZ) is a neurotropic virus. Primary infection with the varicella zoster virus (VZV) often leads to acute varicella which, after recovery remains dormant in the dorsal root ganglia.[1] Age-related decline in immunity or an immunosuppressed condition may lead to the reactivation of VZV causing HZ.[1] VZV latency largely depend on cell-mediated immunity, and reactivation is considered a result of loss of such immune surveillance[2]. Herpes Zoster, when present in patients with comorbid conditions like COPD can be severely debilitating because of the associated immunosuppression and complications. However, there have not been many detailed studies to entail an association between herpes zoster and COPD .

# 2. Methods

The research design method of this literature review is an evidence based rapid review. The aim of this review is first to scrutinize and assess all the available articles on HZ and COPD. Standard databases (PubMed and Google Scholar) and literature searches (Google search engine) with relevant titles: ‘Shingles’, ‘Herpes

zoster', 'Herpes zoster vaccine' and 'COPD' from inception were implemented. References were added with the help of the Paperpile tool on Google Docs. Google Docs was used to write and edit the manuscript. Relevant articles were gathered in Google spreadsheet and extracted information was then performed by five authors (A.K.Y, A.B.S, S.S, S.R.S, S.P.)

# 3. HERPES ZOSTER

Cumulative incidence of HZ ranges from 2.9–19.5 cases per 1,000 population and an incidence rate of HZ ranges from 5.23–10.9 cases per 1,000 person-years.[1] Although the exact cause of HZ reactivation is still unknown, many risk factors like female sex, race/ethnicity, family history, COPD, autoimmune diseases (RA, SLE, and inflammatory bowel disease), physical injury, statin use and other comorbidities like chronic kidney disease, diabetes mellitus, asthma, and depression play role in reactivation.[3,4] Incidence of HZ infection is increased in women as compared to men which is due to more social contact with school going children as compared to men or may be due to more healthcare seeking behavior.[5] Black individuals have about half the risk of development of HZ as white individuals, which potentially could be due to differences in genetic risk, access to health care, and/or health care seeking behaviors.Family history is a consistent risk factor as first degree blood relative with history of herpes zoster have 3 fold increased risk of herpes zoster. Patients with autoimmune disease have increased incidence due to regular intake of immunosuppressive medications.[3] The biological mechanism for most risk factors for HZ can be explained by impaired cell mediated immunity[3].

Initially the patient presents with erythematous skin rash of burning pain type in the affected area lasting for more than 2 days later it ulcerates and dries out .In chronic infection, pain may last up to 4 weeks along with dysesthesias, paresthesias and electric shock like sensations.[2]

Despite the availability of highly effective antiviral drugs, Herpes zoster is associated with many complications like postherpetic neuralgia (PHN) which is clinically meaningful pain lasting for more than 90 days after rash onset, herpes zoster ophthalmicus (HZO) which is VZV reactivation along the distribution of the

ophthalmic division of the trigeminal nerve and can occur with or without eye involvement, Ramsay Hunt syndrome, Bell's palsy and transverse myelitis.[6]

# 3. COPD

## 3.1 PREVALENCE

According to the latest analysis done by Adeloye et al., the global prevalence of COPD was 10.3% in 2019 including 391.9 million cases among people aged 30-79 years based on GOLD definition.[7] The results also showed that COPD was considerably higher in males compared to females (more than double), increased with advancing age and was also higher in Lower Middle Income Countries than High Income Countries.[7] Global Burden of Disease study 2010 showed that COPD was responsible for about 5% of global disability adjusted life years and 5% of total deaths.[8]

## 3.2 PATHOPHYSIOLOGY

Tissue damage causes release of Damage Associated Molecular Patterns (DAMPs) which activate Pattern Recognition Receptors (PRR) resulting in production of inflammatory cytokines and Nucleotide-binding oligomerization Domain like Receptor (NLR)P3 inflammasome.[9] (NLR)P3 inflammasome causes secretion of Interleukins which activate neutrophils, macrophages, helper T1 and Th17 lymphocytes causing airway inflammation.[9] Alveolar macrophages secrete tumor necrosis factor-α which activates adhesion molecules on endothelial cells and also produces reactive oxygen species, metalloproteinases and cathepsins which destroys alveolar structures, promotes mucus production and induces mediators of fibrosis for airway remodeling.[10] In COPD, neutrophil apoptosis is inhibited which causes neutrophil induced inflammation and neutrophil elevation is directly proportional to COPD severity.[9]

Cigarette smoking is the most common etiology leading to COPD.[9] Cigarette smoking disrupts the balance between oxidants and antioxidants which leads to airway inflammation and release of various oxidants such as hydrogen peroxide, nitric oxide, lipid peroxidases which persist even after one stops smoking and leading to damage of lung tissue.[9] Necroptosis is a type of cell death which occurs in cigarette smoking where mitochondrial autophagy occurs and this leads to persistent inflammation and death of airway epithelial cells.[9]

## ROLE OF STEROIDS IN COPD

According to a study done by Yang et. al, the adjusted hazard ratio (HR) of herpes zoster was slightly greater for patients with COPD using inhaled corticosteroids only (HR 2.09) and was even greater for those with COPD using oral steroids (adjusted HR 3.00).[11] This may be due to the immunosuppressive effect of corticosteroids and may also indicate a severe form of COPD rendering them susceptible to HZ.[11] The reason for oral steroids having more hazard ratio than inhaled may be because of greater immunosuppressive effect by oral steroids compared to inhaled steroids.[11]

The results are also supported by another study done which showed a 45% risk of HZ among COPD patients and 61% risk among those with COPD and taking inhaled corticosteroids. Increased outpatient visits, length and number of hospitalizations as depicted in this study also suggests the impact of HZ on underlying COPD.[12]

## 4. COPD AND HERPES ZOSTER

Chronic Obstructive Pulmonary Disease has proven to be a risk factor for Herpes Zoster with an increase in incidence for all age groups varying between 10% - 45% depending on the study.[12–14] One such study by Thompson-Leduc et. al concluded that incidence of HZ in patients with COPD was four times greater than without COPD.[14] Similarly, complications contributed by herpes zoster like postherpetic neuralgia were also higher in patients with COPD.[14] A post hoc analysis has shown that the incidence rate of COPD exacerbations among the COPD patients with HZ was higher compared to those without HZ. similarly, the incidence rates of

Transient Ischemic Attack and Stroke were also higher among COPD patients with HZ compared to those without HZ.[15]

In Terms of hazard ratios, the adjusted HR of herpes zoster was slightly greater for patients with COPD using inhaled corticosteroids only (adjusted HR 2.09, 95% CI 1.38–3.16) and was greatest for patients with COPD using oral steroids (adjusted HR 3.00, 95% CI 2.40–3.75).[11]

Munoz-Quiles et. al. in their retrospective study among 2,289,485 patients from 2009 to 2014 concluded that though HZ increased the severity of COPD and the resources consumed for treatment, this increase was not significant statistically however these findings cannot be ignored altogether.[12] Similarly, COPD has been shown to alter the course of HZ with a larger number of patients experiencing long term side effects like postherpetic neuralgia and a incidence contributing to both the disease condition and use of steroids.[11,12]

# 5. VACCINATION

Live attenuated vaccine named Zostavax, Sanofi Pasteur MSD (ZVL) approved in 2006 is injected for the prevention of HZ. It has been proven useful for adults older than 50 years.[12] Zostavax is given one dose subcutaneously ZVL has been approved in fewer than 70 countries and is a part of the national vaccination schedule in only a handful of nations as of 2020; developing nations being the ones with lowest vaccination programs. Adjuvanted Recombinant Zoster Vaccine (Shingrix) is another vaccine which was developed and licensed in 2017.[12] Shingrix is given in two doses 2-6 months apart intramuscularly. Herpes Zoster vaccine is expensive so must be mainly targeted to the high risk population among which age as a risk factor comes first.[13]

Vaccine effectiveness reduces with increased age. This statement is supported by an RCT done among 22,000 adults aged 50-59 yrs which showed 69.8% vaccine effectiveness within 1.5 years of immunization with Live Attenuated vaccine.[16] Another clinical trial showed that three year efficacy was highest in adults less than 70 years of age (63.9%) compared to those older than 70 years of age (37.6%).[17]

There was also a study which showed 3 year efficacy of 96.6% among adults of 50-59 yrs, , 97.4% among 60-69 years and 91.3% for 70 years and older. They were vaccinated with Recombinant vaccine against HZV.[18] This showed that

vaccine effectiveness in Recombinant vaccine against HZV is higher than that in Live attenuated vaccine.
HZ vaccination is important as it prevents the reactivation of latent HZ and reduces the complications related to the infection.

# 6. ECONOMIC ASPECT

The cost burden of HZ among COPD patients is not studied widely; however annual medical costs for COPD in the USA , through a study, was estimated at about $32 billion in 2010.[19] Similarly, HZ and its complications were estimated at $2.4 billion annually in 2015 in the United States.[20] A study showed that among individuals with COPD, healthcare costs per person were $3,756 higher during the first year after Shingles compared to those without Shingles. It also showed that patients with COPD and HZ had more use of medical service during the first year of observation compared to those with COPD and without HZ.[15]
The mean total cost during the first year of observation period was also higher in the COPD patients with HZ compared to those without HZ($4140±$7616 versus $3749±$7954) and the total cost difference was also statistically significant.[15]
While comparing impact on HZ, childhood varicella vaccination appears to be cost effective, however whether adolescent vaccination is more or less cost effective still remains unclear.[21] Cost effectiveness of HZ vaccination depends on chosen age at vaccination, price of vaccine, duration of protection and assumed cost-effectiveness threshold.[21]

# 7. CONCLUSION

The incidence and severity of HZ increases when associated with COPD. HZ in COPD patients leads to its exacerbation whereas COPD leads to a complicated form of HZ.[14] Appropriate pharmacotherapy at appropriate time along with pulmonary rehabilitation, follow up, aftercare, inhaler training and patient education can adequately control COPD[22]. HZ vaccination is useful to prevent the

reactivation of latent HZ and reduce the complications. To decrease the risk of corticosteroid-induced herpes reactivation during COPD treatment in elderly people, utilization of steroid in adjusted dose is highly advisable.

## Declaration of patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.


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None


## Ethical approval

As the case report contains information of the retrospective period, we had obtained exempt for ethical approval from the Institutional ethical committee.

## Conflicts of Interest

There are no conflicts of interest.


## Provenance and peer review

Not commissioned, externally peer-reviewed

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