International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	THE PRICE OF FLAVOR: BRONCHIOLITIS OBLITERANS DUE DIACETYL, VAPING, AND OCCUPATIONAL EXPOSURE
ARTICLE INFO	Katarzyna Krupa, Weronika Głowacz, Anna Daniel, Kacper Jankowski, Aleksandra Maciejczyk, Natalia Kraciuk, Alicja Bury, Karol Bartecki, Julia Błoniecka, Małgorzata Piekarska-Kasperska. (2025) The Price of Flavor: Bronchiolitis Obliterans Due Diacetyl, Vaping, and Occupational Exposure. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3509
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3509
RECEIVED	21 June 2025
ACCEPTED	26 July 2025
PUBLISHED	30 July 2025
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THE PRICE OF FLAVOR: BRONCHIOLITIS OBLITERANS DUE DIACETYL, VAPING, AND OCCUPATIONAL EXPOSURE

Katarzyna Krupa *[KK] (Corresponding Author, Email: katarzyna.m.krupa@gmail.com)*
Wolski Hospital in Warsaw, 01-211 Warsaw, Poland
ORCID ID: 0009-0006-3120-8631

Weronika Głowacz *[WG]*
Czerniakowski Hospital in Warsaw, 00-739 Warsaw, Poland
ORCID ID: 0009-0009-5481-9509

Anna Daniel *[AD]*
Regional Specialist Hospital in Wrocław – Research and Development Centre, 51-124 Wrocław, Poland
ORCID ID: 0009-0003-8752-6610

Kacper Jankowski *[KJ]*
Bielanski Hospital named after Father Jerzy Popiełuszko in Warsaw, 01-809 Warsaw, Poland
ORCID ID: 0009-0000-3722-7805

Aleksandra Maciejczyk *[AM]*
Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, 02-091 Warsaw, Poland
ORCID ID: 0009-0008-5709-0269

Natalia Kraciuk *[NK]*
Independent Public Healthcare Establishment in Wyszków, 07-200 Wyszków, Poland
ORCID ID: 0009-0007-8319-2296

Alicja Bury *[AB]*
Orlowski Hospital in Warsaw, 00-416 Warsaw, Poland
ORCID ID: 0009-0009-2950-8741

Karol Bartecki *[KB]*
University Clinical Centre of the Medical University of Warsaw, 02-097 Warsaw, Poland
ORCID ID: 0009-0006-1863-242X

Julia Błoniecka *[JB]*
Independent Public Healthcare Facility in Garwolin, 08-400 Garwolin, Poland
ORCID ID: 0009-0004-0199-6230

Małgorzata Piekarska-Kasperska *[MP]*
Provincial Specialist Hospital of the name Stefan Cardinal Wyszyński in Lublin, 20-718 Lublin, Poland
ORCID ID: 0000-0001-5055-4923

ABSTRACT

Background. Bronchiolitis obliterans (BO), or "popcorn lung," is a rare, irreversible obstructive lung disease involving inflammation and fibrosis of small airways. Initially linked to occupational diacetyl exposure in the food industry, BO is now also associated with environmental toxins, post-transplant complications, and e-cigarette use.
Aim. This review presents current knowledge on BO, focusing on pathogenesis, risk factors, clinical presentation, diagnosis, treatment, and public health implications, particularly concerning e-cigarettes and environmental exposures.
Materials and Methods. A narrative review was performed using PubMed, Scopus, ScienceDirect, and Google Scholar, screening English and Polish-language articles from 2000–2025. Keywords included: "bronchiolitis obliterans," "diacetyl," "e-cigarettes," "vaping," "occupational exposure," and "BO diagnosis." Studies involving humans, relevant animal models, or in vitro analyses were included.
Analysis of Literature. BO often presents with nonspecific symptoms and is commonly underdiagnosed. High-resolution CT and histopathology are key diagnostic tools. While immunosuppressive therapy may help post-transplant patients, it is ineffective in toxin-induced BO. Supportive care, including bronchodilators, oxygen therapy, and rehabilitation, remains the mainstay of treatment. Lung transplantation is a last resort. E-cigarettes pose a growing risk due to vaporized compounds like diacetyl and formaldehyde.
Conclusions. BO remains a serious clinical and public health challenge. With no curative treatment and poor prognosis in many cases, prevention is critical. Regulatory oversight of harmful inhaled substances, particularly in vaping products and occupational environments, alongside public education on associated risks, is essential.

KEYWORDS

Bronchiolitis Obliterans, Popcorn Lung, Diacetyl, E-Cigarettes, Vaping, Occupational Exposure

CITATION

Katarzyna Krupa, Weronika Głowacz, Anna Daniel, Kacper Jankowski, Aleksandra Maciejczyk, Natalia Kraciuk, Alicja Bury, Karol Bartecki, Julia Błoniecka, Małgorzata Piekarska-Kasperska. (2025) The Price of Flavor: Bronchiolitis Obliterans Due Diacetyl, Vaping, and Occupational Exposure. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3509

Introduction.

Bronchiolitis obliterans (BO), often referred to as "popcorn lung," is a rare, chronic lung condition marked by inflammation and progressive fibrosis of the bronchioles, leading to irreversible airway narrowing.[1] It typically presents with nonspecific respiratory symptoms such as dyspnea and reduced exercise tolerance. The disease often begins insidiously, delaying early diagnosis.[2]

The term "popcorn lung" originated after eight cases of BO were identified among former workers of a microwave popcorn factory in Missouri, USA, between 1992 and 2000. Subsequent investigations linked the condition to inhalation exposure to diacetyl, a chemical compound used to provide a buttery flavor. This discovery spurred further research into the toxicity of flavoring chemicals and occupational hazards in the food and chemical industries.[3]

In recent years, the rising popularity of e-cigarettes has raised concerns about bronchiolitis obliterans in users, as many flavored e-liquids contain diacetyl or its derivatives. Simultaneously, environmental and occupational exposures remain significant risk factors. This positions BO as an important issue in both clinical and public health contexts.

Aim

This review aims to present the current understanding of the pathogenesis, causes, and risk factors of bronchiolitis obliterans, with particular attention to e-cigarette exposure and environmental toxins. It also outlines current approaches to diagnosis, treatment, and prevention.

Material and methods

This narrative review was conducted to synthesize current scientific knowledge on bronchiolitis obliterans (BO), with an emphasis on its toxicological, environmental, and clinical aspects. A structured literature search was carried out between May and June 2025 across several electronic databases, including PubMed, Scopus, ScienceDirect, and Google Scholar.

The following keywords and Boolean combinations were used: "bronchiolitis obliterans", "popcorn lung", "diacetyl", "e-cigarettes", "vaping", "inhalational toxins", "occupational exposure", "BO diagnosis", "BOS post-transplant", and "bronchiolar fibrosis." Search filters included articles published in English or Polish between 1998 and 2025.

Inclusion criteria:

- Peer-reviewed original research articles, clinical studies, review articles, and case reports.
- Publications focusing on the etiology, pathophysiology, diagnosis, treatment, or prevention of BO.
- Studies involving human subjects and relevant animal or in vitro models.

Exclusion criteria:

- Non-scientific publications, commentaries, and editorials without data or systematic analysis.
- Studies focusing exclusively on transplant rejection without BO confirmation.

The literature was critically reviewed and selected based on relevance to the aim of the paper.

Analysis of literature

Pathophysiology

Bronchioles are small airways measuring 0.5–1 mm in diameter. They divide into terminal and respiratory (alveolar) bronchioles, which connect to alveoli where gas exchange occurs. Their walls comprise a single-layer ciliated epithelium (without goblet cells), spiral muscle fibers, and a thin fibrous membrane devoid of cartilage.[5]

In bronchiolitis obliterans, chronic inflammation of the bronchioles causes progressive narrowing. It begins with epithelial injury due to toxic, infectious, or immunologic agents. Inflammatory cells are activated, stimulating fibroblasts to overproduce collagen and other extracellular matrix components. With sustained exposure, repeated epithelial injury and persistent inflammation lead to thickened bronchiole walls and narrowed lumens, resulting in airflow obstruction and impaired pulmonary function.[2,6]

Causes and Risk Factors of Bronchiolitis Obliterans Development

Occupational Exposure: Toxins and Chemicals

A key cause of bronchiolitis obliterans is inhalational exposure to diacetyl (2,3-butanedione), a volatile compound with a buttery aroma used in food flavoring. 2,3-pentanedione, a chemical analog of diacetyl, also exhibits respiratory toxicity.[6] Workers in popcorn production, coffee roasting facilities, and food manufacturing involving products like sour cream or vegetable-based spreads are at risk.[2,3,7–9]

BO has also been reported in World Trade Center survivors and responders, and in U.S. military personnel deployed to Southwest Asia and Afghanistan, exposed to desert dust and burn pits. Isolated cases have been linked to thionyl chloride, fly ash, styrene, and powders used in photocopying.[2]

E-Cigarette Exposure

E-cigarettes vaporize a nicotine solution containing flavorings rather than burning tobacco.[10] The aerosol they produce contains compounds like diacetyl, acetaldehyde, acetylpropionyl, acetoin, and propylene glycol, which can degrade into diacetyl and formaldehyde when heated.[11–14] Studies have detected at least one flavoring agent in 92% of tested e-liquids.[13] Vaping-related cases of BO have been documented,[4,15,16] underscoring the need for further research and regulatory oversight.

Other Risk Factors

Additional risk factors for bronchiolitis obliterans include viral infections (e.g., adenovirus, RSV, *Mycoplasma pneumoniae*), connective tissue diseases (especially rheumatoid arthritis), and medications such as penicillamine. BO is also a known complication of lung, heart-lung, and hematopoietic stem cell transplants.[17,18] In some cases, its origin is idiopathic.[19]

Clinical Presentation and Diagnostics

Clinical Symptoms

Bronchiolitis obliterans typically has an insidious onset with gradually worsening symptoms: exertional dyspnea progressing to rest dyspnea, dry cough, respiratory insufficiency, and occasionally wheezing. In some cases—especially post-transplant or post-viral—symptoms may appear more acutely. [2,17]

Diagnostic Methods

Diagnosis is based on clinical symptoms, imaging, lung function tests, and often histopathological confirmation. Chest X-rays may appear normal or nonspecific, whereas high-resolution CT (HRCT) is the imaging method of choice. Characteristic findings include mosaic attenuation, air trapping, alveolar hyperinflation, hypoxic vasoconstriction, bronchial wall thickening, centrilobular opacities, central bronchiectasis, and atelectasis.[17,20,21]

Spirometry may initially appear normal but later reveals irreversible airway obstruction with decreased FEV1, reduced FEV1/VC ratio, and decreased MEF25. Post-bronchodilator response is minimal. Plethysmography may show elevated residual volume (RV) and RV/TLC ratio.[21]

Lung biopsy, preferably transthoracic or sometimes transbronchial, is often required for definitive diagnosis. Two forms of bronchiolitis obliterans are recognized histologically: constrictive and proliferative. Constrictive BO involves peribronchiolar inflammatory infiltrates leading to airway deformation and subepithelial fibrosis. Proliferative BO features intraluminal polypoid formations (Masson bodies), which may occlude airways and resemble butterfly wings microscopically.[22]

Environmental and occupational bronchiolitis obliterans typically presents with the constrictive variant.[2] Due to patchy airway involvement and variable inflammation, biopsies carry a risk of sampling error, reducing diagnostic sensitivity.[21]

Differential Diagnosis

Due to nonspecific symptoms and the rarity of BO, other causes of chronic airway obstruction must be excluded, including COPD, asthma, bronchogenic carcinoma, interstitial lung diseases, cystic fibrosis, recurrent aspiration, and previous pulmonary embolism. A detailed history of exposures, infections, autoimmune diseases, and transplant history is essential.[23]

Treatment and Prognosis

Treatment

Bronchiolitis obliterans is a progressive disease with no definitive cure. Treatment focuses on symptom management and disease progression delay. No universally accepted treatment protocol exists.[22]

Immunosuppressants, especially systemic glucocorticosteroids like prednisone, are commonly used, particularly in post-transplant cases. Their efficacy is variable and not consistently supported by robust evidence. Long-term use carries risks such as hypertension, hyperglycemia, and osteoporosis.[24]

Other immunosuppressants like tacrolimus, cyclosporine, and mycophenolate mofetil are often used post-transplant.[22] Inhalation-related bronchiolitis obliterans generally does not respond to immunosuppressants; removing the offending agent is crucial.[23]

Supportive care includes pulmonary rehabilitation, oxygen therapy for hypoxemia, influenza and pneumococcal vaccinations, and antibiotics during infectious exacerbations.[22] Azithromycin combined with fluticasone and montelukast has shown benefit in post-HSCT BO. For toxin-induced BO, bronchodilators, antitussives, and oxygen therapy are used.[23]

In advanced stages, lung transplantation may be the only option, though it is reserved for select cases due to high complication rates and lifelong immunosuppression requirements.[22,23,25]

Prognosis

The prognosis for BO is generally poor. Idiopathic and environmental forms respond less to treatment. Outcomes depend on disease progression and supportive therapy effectiveness. Post-transplant BO (BOS) is a leading cause of long-term mortality in lung recipients.[22,23]

Prevention and Public Health Implications

Given the irreversibility of bronchiolitis obliterans and limited treatment options, prevention is essential at both individual and systemic levels. This involves reducing exposure to known risk factors, particularly in occupational and consumer environments.

In industries such as food, chemical, and plastics manufacturing, enforcing occupational safety standards and ventilation is critical. Substances like diacetyl, 2,3-pentanedione, and industrial dusts should be strictly controlled.[2,3] Employers must provide personal protective equipment and periodic health screenings.[7–9]

Consumer product oversight is equally vital. Despite being marketed as safer alternatives, many e-cigarettes emit toxic aerosols, including diacetyl.[11,13,14] The lack of standardized limits for e-liquid ingredients poses a public health risk. In 2016, the American Lung Association urged the FDA to ban diacetyl and related compounds.[26] The FDA now assesses product safety but lacks a fixed list of banned substances.[27]

In contrast, the EU's Tobacco Products Directive (TPD) enforces stricter ingredient regulations, including a diacetyl ban. However, enforcement varies across member states, and oversight remains inconsistent.[28,29, 30]

Health education is crucial, especially targeting youth and e-cigarette users. Awareness campaigns should communicate the toxic potential of inhaled substances, even those marketed as "healthier" alternatives.[31]

Conclusions

Bronchiolitis obliterans (BO) is a serious, progressive condition marked by irreversible damage to the small airways. While historically linked to occupational diacetyl exposure, increasing evidence implicates e-cigarettes, environmental toxins, and post-transplant complications.

Its vague symptomatology and diagnostic challenges necessitate comprehensive evaluation, including detailed exposure histories and histopathology. Immunosuppressive therapies show limited success, especially in non-transplant cases.

Public health efforts should prioritize prevention through regulation, education, and surveillance. Further research and coordinated efforts across medical, legislative, and educational domains are essential to mitigate risk and improve patient outcomes.

Disclosure

Funding: This study did not acquire external funding.

Author contributions

Conceptualization: K.K; Methodology: W.G; Validation: K.J. and A.D.; Formal Analysis: A.M.; Investigation: JB.; Data Curation: M.P.; Writing – Original Draft Preparation: K.K., W.G., and K.B.; Writing – Review & Editing: J.B., A.B. and N.K.; Visualization: J.B.; Supervision: K.K. and W.G.; Project Administration: A.M.

All authors have read and agreed with the published version of the manuscript.

Conflicts of interest: The authors declare no conflict of interest.

Data availability: Not applicable.

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