



# A breath of not so fresh air...

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Despite being widely used as a recreational drug, “poppers” lack a legal framework for their delivery. Their composition may vary largely. This report describes a case of severe bronchiolitis following amyl nitrite mixture inhalation. <https://bit.ly/3p3S7LM>

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A 23-year-old woman presented to the emergency department with acute onset respiratory symptoms consisting of chest discomfort, breathlessness and dry cough. She had no relevant past medical history, did not take any medication and did not smoke tobacco or cannabis.

This was her second visit to the emergency department with the same complaints. On her first visit, earlier that day, the patient had a normal physical examination and chest radiograph. Fit for discharge, the patient was sent home while waiting for her severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result.

On the second hospital admission, the patient had a normal lung auscultation contrasting with a transcutaneous oxygen saturation ( $S_{pO_2}$ ) of only 91% on room air. Her respiratory rate was 20 breaths per min, her heart rate was 100 beats per min and her axillary temperature 36.0°C.

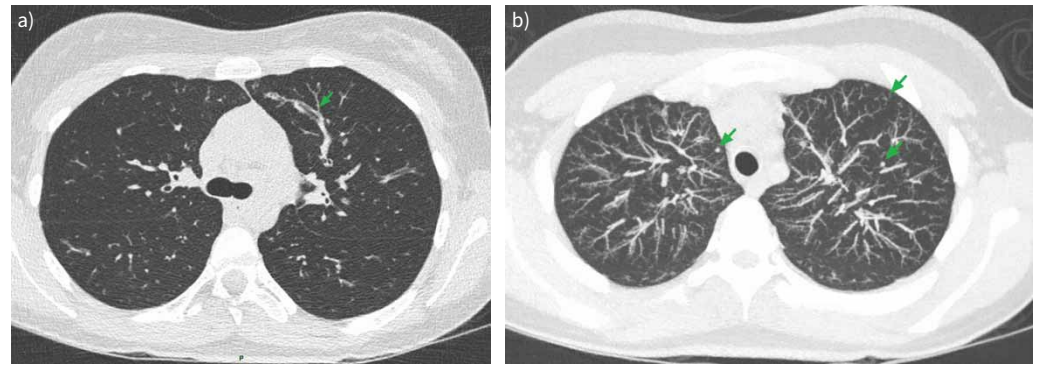
Initial work-up revealed mild inflammation (C-reactive protein (CRP) 35.3 mg·dL<sup>-1</sup>, with a normal value <5), with a leukocyte count of 6.01×10<sup>3</sup> per μL, eosinophil count of 0.37×10<sup>3</sup> per μL and D-dimer value of 431 ng·mL<sup>-1</sup>. The nasopharyngeal PCR testing for SARS-CoV-2 RNA was negative. Results of arterial blood gases analysis are displayed in (table 1).

A high-resolution computed tomography (HRCT) without contrast enhancement was performed (figure 1).

TABLE 1 Results of arterial blood gases

Parameter	Patient value	Normal range
pH	7.40	7.35–7.45
Carbon dioxide tension, mmHg	36	35–45
Oxygen tension, mmHg	66	85–95
HCO <sub>3</sub> <sup>-</sup> , mmol·L <sup>-1</sup>	22	22–28
Oxyhaemoglobin, %	90.8	70–100
Methaemoglobin, %	0.2	0.0–2.0
Lactate, mmol·L <sup>-1</sup>	0.7	0.5–2.2





**FIGURE 1** Computed tomography on admission.

### Task 1

Describe the chest CT in figure 1.

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### Task 2

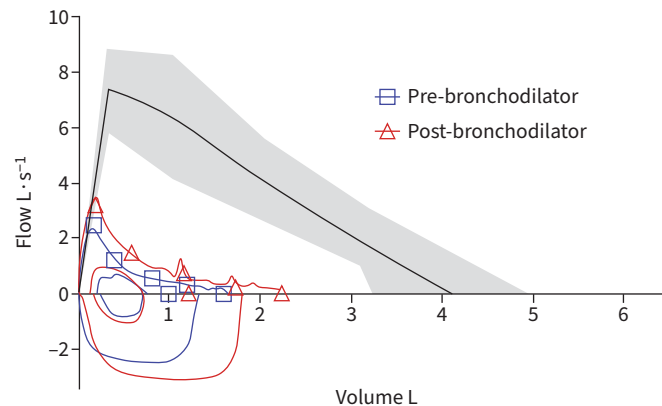
What is your differential diagnosis at this stage?

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After further enquiry, our patient reluctantly reported a dozen inhalations of a recreational drug, commonly known as “poppers”, the night prior to her admission (figure 2).



**FIGURE 2** Isoamyl nitrite mixture sold as “leather cleaner” for legal reasons.



**FIGURE 3** Spirometry and bronchodilator responsiveness testing at admission.

**TABLE 2** Pulmonary function testing at admission

Parameter	Measured	Predicted value	Lower limit	% predicted
FEV <sub>1</sub> (L)	1.00	3.54	2.84	28
FEV <sub>1</sub> /FVC	62.25	84.35	73.64	74
FVC (L)	1.60	4.11	3.28	39
TLC (L)	3.61	5.30	4.31	68
D <sub>LCO</sub> (mL·min <sup>-1</sup> ·mmHg <sup>-1</sup> )	11.14	23.97	18.65	46
D <sub>LCO</sub> /V <sub>A</sub> (mL·min <sup>-1</sup> ·mmHg <sup>-1</sup> ·L <sup>-1</sup> )	4.52	4.69	3.66	96

FEV<sub>1</sub>: forced expiratory in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; V<sub>A</sub>: alveolar volume.

Pulmonary function tests (figure 3 and table 2) revealed a mixed ventilatory defect with a forced expiratory volume in the first second (FEV<sub>1</sub>) of 1 L (28% of predicted value) and a total lung capacity (TLC) of 3.61 L (68% of predicted value). Forced vital capacity was of 1.6 L (39%). Residual volume/TLC ratio was 206% of the predicted value. Obstruction was reversible following bronchodilation (administration of salbutamol 400 µg). Fractional exhaled nitric oxide (F<sub>ENO</sub>) was within normal range.

The diagnosis of acute toxic bronchiolitis was established based on clinical signs, HRCT pattern and pulmonary function tests.

A bronchoscopy failed to reveal any endobronchial anomalies. Bronchoalveolar lavage composition presented a high eosinophil count (28%), along with 36% macrophages, 21% lymphocytes, 13% neutrophils and 2% epithelial cells. Endobronchial biopsies demonstrated eosinophilic infiltration in the mucosae.

### Task 3

How would you treat this patient?

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A short course of oral methylprednisolone (32 mg for 5 days) resulted in progressive clinical improvement. On the fifth day of her stay, our patient's clinical state had already greatly improved and the patient was discharged the next day (figure 4 and table 3).

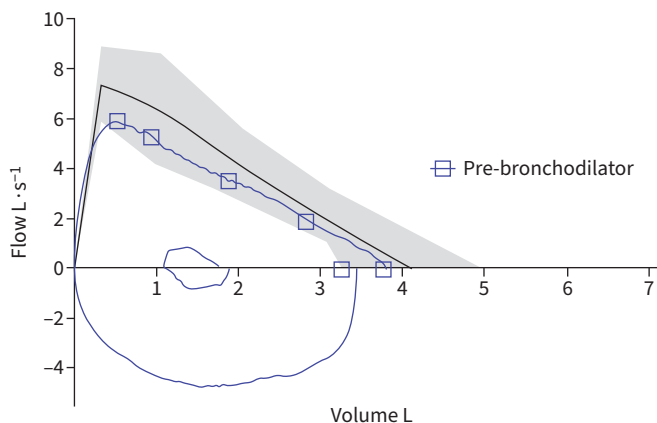


FIGURE 4 Spirometry on day 5.

TABLE 3 Pulmonary function testing on day 5

Parameter	Measured	Predicted value	Lower limit	% predicted
FEV <sub>1</sub> (L)	3.26	3.54	2.84	92
FEV <sub>1</sub> /FVC	86.47	84.35	73.64	103
FVC (L)	3.77	4.11	3.28	92
TLC (L)	4.85	5.30	4.31	92
D <sub>LCO</sub> (mL·min <sup>-1</sup> ·mmHg <sup>-1</sup> )	19.28	23.97	18.65	80
D <sub>LCO</sub> /V <sub>A</sub> (mL·min <sup>-1</sup> ·mmHg <sup>-1</sup> ·L <sup>-1</sup> )	4.27	4.69	3.66	91

FEV<sub>1</sub>: forced expiratory in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; V<sub>A</sub>: alveolar volume.

#### Task 4

If a toxic origin is suspected, which substances could be responsible for respiratory effects after “poppers” use?

- Isomers of amyl nitrite
- Diacetyl
- Derivatives of butanol
- Nitrous oxide
- Nitrogen dioxide

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#### Discussion

Bronchiolitis seldom affects adults and is most often seen in younger patients following a viral infection [1]. At older ages, viral infections remain the most common aetiology along with inhalational injuries. Although many different categorisations have been proposed [2–5], no consensual classification exists today.

The equivocal term bronchiolitis encompasses many different disease processes (table 4) [6, 7]. The timeframe is also very variable: some aetiological agents will induce an acute or chronic disease, or even both.

Usually, bronchiolitis will be responsible for dry cough and breathlessness. Other typical symptoms include chest discomfort and haemoptysis. Lung function tests will usually show non-reversible obstruction, hyperinflation and diffusing capacity of the lung for carbon monoxide (D<sub>LCO</sub>) reduction, although restrictive, mixed or reversible defects are not unusual [12]. Radiologists confronted with bronchiolitis will frequently describe features such as mosaic pattern secondary to air trapping, bronchial wall thickening, centrilobular nodules, branching linear opacities and bronchiolar dilatation [5, 13]. A lung biopsy might help obtain a definitive diagnosis, but once again, pathological findings are nonspecific and

TABLE 4 Disease processes encompassed by the term bronchiolitis

Infectious	Toxic	Autoimmune	Cryptogenic/miscellaneous
Respiratory viruses, such as the respiratory syncytial virus, influenza and parainfluenza	Smoke-related and e-cigarette or vaping use-associated lung injury (EVALI)	Bronchiolitis obliterans syndrome (BOS) seen in chronic lung allograft dysfunction	Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
Parasitic	Diffuse aspiration bronchiolitis	Sjögren syndrome	Langerhans histiocytosis
Fungal	Nitrogen dioxide (NO <sub>2</sub> ) inhalation	Paraneoplastic	Follicular bronchiolitis
Mycobacterial	Mustard gas (sulfur mustard)	Rheumatoid arthritis	Panbronchiolitis
<i>Mycoplasma pneumoniae</i>	Ingestion of <i>Sauropus androgynus</i>	Systemic lupus erythematosus	Eosinophilic bronchiolitis
Allergic bronchopulmonary mycosis	Diacetyl (popcorn plant workers)	Inflammatory bowel disease-related bronchiolitis	COPA syndrome
Information from [8–11].			

ill-defined. They usually consist of inflammatory changes such as peribronchiolar mononuclear infiltrates, fibrosis, broncho- and bronchiolectasies [14].

Concerning the clinical case described here, there is an obvious history of toxic exposure preceding hospital admission. The low blood eosinophil count along with the favourable clinical response to corticosteroids does not fit the alternative diagnosis of eosinophilic bronchiolitis. We excluded other differential diagnoses by means of serological tests, autoimmune serologies, transbronchial biopsy, cultures and respiratory panel multiplex in the bronchoalveolar lavage fluid.

One of the most infamous toxic-related bronchiolitis is an occupational condition called silo-filler's disease. First described as early as in the 1800s, it results from the inhalation of nitrogen dioxide (NO<sub>2</sub>). NO<sub>2</sub> starts building up a few hours after the silo is filled and can reach levels of 200–2000 ppm. When in contact with water, NO<sub>2</sub> turns into the corrosive nitrous acid. Its inhalation can result in acute, permanent and/or even life-threatening injury. Some cases of chronic exposure resulting in bronchiolitis obliterans have also been reported [5, 14–16]. NO<sub>2</sub> toxicity has also been described in other settings such as in poorly ventilated combustion areas or indoor ice rinks [17].

Contrasting with the toxicity of inorganic nitrogen inhalation, exposure to organic derivatives appears less directly toxic for the lungs. As there is no legal framework for their delivery, the composition of “poppers” may vary largely. They belong to the family of aliphatic or cyclic alkyl nitrites. Usually, they are based on amyl, isopropyl or butyl nitrites. Although some moderate irritating effects could be observed on the eye, skin or lung, inhalation of “poppers” is almost never associated with lung toxicity, and not with bronchiolitis obliterans. Accidental aspiration of liquid amyl or butyl nitrite has caused lipoid pneumonia [18]. Methaemoglobinaemia is a possible complication of “poppers” inhalation but might be difficult to detect after a significant delay, such as in the present observation.

Also of note, another component was mentioned on the “poppers” bottle brought by the patient: 3-methyl-1-butanol (3MB), a microbial volatile organic compound (MVOC), that could be considered as a mild irritant. The fact that the patient reported no nasal or eye irritation reduces the likelihood of a 3MB toxicity [19].

Recently, outbreaks of e-cigarette or vaping use-associated lung injury (EVALI) have brought toxic inhalations back into the medical community spotlight. The umbrella term EVALI encompasses very distinct pathological and radiographic features (e.g. diffuse alveolar damage, acute eosinophilic pneumonia, lipoid pneumonia) [18, 20, 21].

As of today, no single trigger has been identified as being a sufficient condition for the occurrence of such a disorder, although some suspicion exists regarding the use of products such as vitamin E acetate, medium chain triglycerides, heavy metals and tetrahydrocannabinol [21, 22]. Criteria for the diagnosis of EVALI usually include the presence of constitutional or gastrointestinal symptoms that were absent in our clinical picture.

The scientific evidence supporting specific treatment of toxic inhalations is disappointing and at best provided by some case series. Corticosteroids seem to be the only effective treatment against nitrogen dioxide exposure with clinical, functional and radiological partial or full recovery [23, 24]. The timing and the dose of the glucocorticoid administration is not standardised although it is hypothesised that an early administration reduces the risk of further complications [24]. This beneficial effect of glucocorticoids does not seem as spectacular in other exposure-related lung diseases, such as inhalation of diacetyl seen in popcorn plant workers, textile workers suffering from Ardystil syndrome [25, 26] or inhalation of mustard gas [20]. Other therapies for inhalational bronchiolitis have been investigated such as N-acetyl cysteine, cyclophosphamide, azithromycin and bronchodilators with no strong proof of a beneficial effect.

Regardless of the aetiological agent, the severity of the inhalational injury seems dose-related, thus exposure cessation is essential. Supportive treatment should also be provided. Lung transplantation remains as a last line of treatment in cases of severe respiratory insufficiency.

After an empiric treatment by methylprednisolone, our patient presents a full recovery. No relapse occurred on follow-up.

### Answer 1

The chest CT scan revealed some nonspecific findings of multiple micronodules such as the one that can be seen in the right upper quadrant of the image; diffuse bronchial wall thickening (figure 1a), hyperinflation and the presence of endobronchial impactions.

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### Answer 2

The clinical and radiological picture is compatible with an acute bronchiolitis, a nonspecific term used to describe the inflammation and the resulting airflow obstruction of small airways. The most common aetiological agents in adults are viral infections and inhalational exposure.

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### Answer 3

Exposure cessation is essential. Supportive care such as oxygen therapy should be provided in case of hypoxaemia. Based on a previous case series in the literature, treatment with methylprednisolone was initiated.

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### Answer 4

Correct answers: a and c. As the exact composition of “poppers” may vary, users are mainly exposed to isomers of amyl nitrite and to some organic solvents (e.g. butanol derivatives). “Poppers” may be a source of nitrous oxide and caution should be exerted with medications using this pathway.

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Conflict of interest: None declared.

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