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Adverse reactions and safety of nebulized budesonide in elderly patients with inflammatory airway diseases

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Abstract: **Background**: Budesonide suspension is a first-line inhaled corticosteroid for elderly patients with inflammatory airway diseases, but existing research lacks targeted safety data for the very elderly (≥80 years), systematic analysis of adverse reaction (ADR) temporal distribution and quantitative evidence for modifiable clinical risk factors. **Objective**: To investigate the safety profile, ADR temporal patterns and independent modifiable risk factors of nebulized budesonide suspension in elderly patients, with a focus on ≥80 years. **Methods**: A retrospective analysis of 128 elderly patients (39 ≥80 years) treated with budesonide suspension (2 ml:1 mg) from January 2023 to June 2025 was conducted. ADRs were identified via medical record cross-check and verified by an expert team, with causality assessed using the WHO-UMC system. ADR incidence, type and temporal distribution were observed; univariate and multivariate logistic regression analyses were used to screen independent risk factors. **Results**: The overall incidence of mild ADRs was 17.97%, with local ADRs (78.26%, predominantly oropharyngeal candidiasis) and systemic ADRs (21.74%). ADRs peaked at 8–14 days (39.13%). Age ≥80 years (OR=3.245, p=0.030), treatment duration >14 days (OR=2.897, p=0.048) and inadequate mouth rinsing (OR=4.126, p=0.008) were independent risk factors. ADR incidence was higher in patients with ≥3 underlying diseases (25.00% vs. 11.76%). **Conclusion**: Nebulized budesonide suspension is well tolerated in elderly patients, with no severe ADRs. This study clarifies temporal patterns of ADRs and identifies inadequate mouth rinsing as a key modifiable risk factor, providing targeted safety data for the very elderly. Standardized mouth rinsing and short-course medication are recommended for high-risk groups to reduce ADR risk. Notably, this study is limited by its single-center, retrospective design, which may introduce selection and information bias and the findings require validation in prospective multi-center studies with larger sample sizes.

Keywords: Adverse reactions; Budesonide suspension; Elderly patients; Nebulized inhalation

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INTRODUCTION

The accelerating aging of the population has led to a year-on-year increase in the incidence of inflammatory airway diseases in the elderly (including bronchial asthma, COPD, chronic bronchitis), which have become a major category of respiratory diseases threatening geriatric health (Xuqing *et al.*, 2026; Olszanecka Glinianowicz *et al*., 2021). Inhaled corticosteroids (ICS) are the cornerstone of clinical treatment for these diseases due to their strong targeting and low systemic bioavailability and budesonide suspension—a first-line ICS with over 90% hepatic first-pass metabolism—is theoretically suitable for elderly patients with declining physiological function, yet its clinical safety in this population still needs further verification (Jian *et al*., 2024; Peiqin *et al*., 2025). Elderly patients exhibit unique pathophysiological characteristics that may increase ADR risk, including age-related declines in drug metabolism and clearance, impaired oropharyngeal mucosal barrier function and high prevalence of underlying diseases and polypharmacy, which may alter budesonide's pharmacokinetic characteristics (Jaycie and Kimberly , 2025; Yuran *et al*., 2025).

Existing clinical research has obvious limitations and three critical unaddressed knowledge gaps that restrict the precision of clinical medication for the elderly: First, most studies focus on young and middle-aged populations and lack specific safety data for the very elderly (≥80 years), failing to meet the needs of stratified precision medicine for the elderly (Dong Won *et al*., 2024); Second, most studies only report the overall incidence of ADRs but lack systematic analysis of their temporal distribution and onset patterns, leaving the high-risk time window of ADRs unclear and resulting in blind clinical monitoring; Third, existing evidence lacks quantitative confirmation of the independent risk effects of modifiable factors such as inadequate mouth rinsing on ADRs and the synergistic effect of such factors with advanced age and long-term medication has not been elucidated, making it difficult to formulate targeted clinical prevention and control strategies. In addition, there is a lack of safety research on

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budesonide suspension from a specific manufacturer and specification (2 ml: 1 mg) in the elderly, which is commonly used in primary clinical practice in China, leading to a shortage of targeted references for clinical use.

This study hypothesizes that age ≥80 years, treatment duration >14 days and inadequate mouth rinsing are independent risk factors for budesonide-related ADRs in the elderly and that ADRs in this population exhibit distinct temporal distribution characteristics. We conducted a retrospective analysis of 128 elderly patients (including 39 cases ≥80 years) treated with budesonide suspension (2 ml: 1 mg) from January 2023 to June 2025, aiming to systematically investigate the safety profile, temporal patterns of ADRs and independent modifiable risk factors, with a focus on the very elderly. This study seeks to fill the above-mentioned knowledge gaps, provide targeted stratified safety evidence for the elderly population and offer a scientific basis for standardized clinical medication and ADR prevention in clinical practice.

MATERIALS AND METHODS

General information

A retrospective study was conducted on 128 elderly patients who received budesonide suspension nebulization therapy at the Department of Geriatric Psychiatry, Shaoxing Seventh People's Hospital, from January 2023 to June 2025.

Inclusion criteria

(1) Age ≥ 60 years;
(2) Meets the diagnostic criteria for bronchial asthma, acute exacerbation of COPD, or acute exacerbation of chronic bronchitis as defined in the *Guidelines for the Prevention and Treatment of Bronchial Asthma (2024 Edition)* (Jianjun and Qianxi , 2025), *Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2021 Revised Edition)* (Jia *et al*., 2025), or *Internal Medicine (9th Edition)* (Bin *et al*, 2025);
(3) Used budesonide inhalation suspension (specification: 2ml: 1mg, National Drug Approval Number: H20213286, batch number: SA25230) manufactured by Sichuan Prite Pharmaceutical Co., Ltd.;
(4) Complete clinical data, including baseline data, medication records, laboratory tests and adverse reaction follow-up records;
(5) Treatment duration ≥ 3 days, with follow-up up to 7 days after discontinuation of medication.

Exclusion criteria

(1)Hypersensitivity to budesonide or its excipients;
(2) Pre-existing oral oropharyngeal candidiasis, severe hepatic/renal insufficiency (ALT/AST > 3ULN, serum creatinine > 2ULN) – excluded for altered budesonide metabolism/clearance confounding ADR causality;
(3) Concomitant use of oral/intravenous corticosteroids – excluded for overlapping systemic steroid effects that cannot distinguish nebulized budesonide-specific ADRs;
(4) Mid-treatment hospital transfer, self-discontinued medication, or interrupted follow-up;
(5) Cognitive impairment precluding cooperation with rinsing or follow-up procedures.

Administration method

All patients received nebulized inhalation therapy using a PARI BOY SX air compressor nebulizer. Dosage was adjusted by disease severity: mild cases (1 mg twice daily); moderate-severe cases (2 mg twice daily, tapered to 1 mg twice daily after symptom stabilization). Nebulization time: 10-15 minutes per session. Adherence monitoring was conducted via medical record review of nebulization execution records and nursing notes; patients with ≥80% nebulization completion rate were deemed adherent. After inhalation, patients were instructed to rinse mouths with water 3 times (≥30 seconds each). Standardized mouth rinsing was objectively defined as strict compliance with the above procedure (documented in nursing records); non-standardized rinsing was defined as occasional/no rinsing, or incomplete rinsing (no record of compliance/verbal report of non-adherence). The treatment course was 3-28 days.Adherence and mouth rinsing practice were assessed retrospectively via medical record review of nebulization execution records and nursing notes—an approach with inherent subjectivity due to reliance on the completeness and standardization of clinical documentation, a limitation explicitly acknowledged in this study.

Observation indicators and judgment criteria

The observation period is from the start of medication to 7 days after discontinuation. Specific observation indicators are as follows:

Baseline data

Gender, age, body mass index (BMI), smoking history (≥10 years of smoking and ≥10 cigarettes per day defined as a smoking history), type and number of underlying diseases, indications for medication, initial dose, duration of treatment, whether oral rinsing was performed correctly, types of concomitant medications, baseline levels of liver and kidney function and immune function indicators ($CD4^+/CD8^+$ ratio).

Adverse reaction monitoring

The observation period was from medication initiation to 7 days after discontinuation. ADRs were identified via cross-review of electronic medical records (admission notes, daily records, nursing notes, laboratory reports) by two trained researchers; verification was conducted by a senior respiratory physician and a clinical pharmacist.

Causality between adverse events and budesonide was assessed using the WHO-UMC pharmacovigilance system, with only "probable/possible" ADRs included in statistical analysis. ADRs were classified by type (local/systemic) and graded for severity (CTCAE 5.0 standard) (Lei *et al*., 2025), with detailed records of onset time, treatment and outcome.

Laboratory indicators

The overall impact of the drug on the patient is assessed by measuring blood glucose, liver and kidney function, complete blood count and immune function before and after medication.

Statistical analysis

Data were processed using SPSS 26.0 statistical software. Quantitative data were expressed as mean ± standard deviation and independent-samples t-tests were used for comparisons between groups. Categorical data were expressed as number of cases (rates) [n (%)] and χ^2 tests were used for comparisons between groups. Exposure-adjusted ADR incidence was calculated as the total number of ADR events divided by total budesonide exposure patient-days; time-to-event analysis was used to estimate the median time to first ADR onset and its 95% confidence interval. A multivariate logistic regression model was adjusted for clinically relevant covariates, including underlying respiratory diagnosis, disease severity, initial budesonide dose, treatment duration and concomitant respiratory medications, to control for confounding bias.Variables with $p < 0.05$ in univariate analysis were included in the multivariate logistic regression model to screen for independent risk factors for adverse reactions. $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics (age, gender, diagnosis, disease severity, comorbidities, budesonide dosage, treatment duration, mouth rinsing practice) were comparable between patients with and without adverse reactions (ADRs). Chi-square tests and independent t-tests showed no significant differences in all baseline variables (all $p > 0.05$), indicating good baseline equivalence and excluding confounding bias from heterogeneous clinical features for subsequent ADR risk analysis.

Medication indications

Budesonide nebulization was used for bronchial asthma (45 cases, 35.16%), acute exacerbation of COPD (58 cases, 45.31%) and acute exacerbation of chronic bronchitis (25 cases, 19.53%), consistent with the real-world clinical application of inhaled corticosteroids (ICS) for elderly patients with inflammatory airway diseases. The most common underlying diseases were hypertension (48 cases, 37.50%), diabetes (32 cases, 25.00%), coronary heart disease (29 cases, 22.66%) and cerebrovascular disease (21 cases, 16.41%). A total of 12 cases (9.38%) had no underlying diseases, 56 cases (43.75%) had 1–2 types and 60 cases (46.87%) had ≥3 types—reflecting the high multimorbidity rate in elderly patients, a key clinical background for ADR risk assessment.

Medication-related information

The treatment course ranged from 3 to 28 days (mean: 11.24±5.36 days), with 91 cases (71.09%) ≤14 days and 37 cases (28.91%) >14 days. Standard mouth rinsing was performed in 82 cases (64.06%) and inadequate rinsing in 46 cases (35.94%). The initial dose was 1 mg/dose in 85 cases (66.41%) and 2 mg/dose in 43 cases (33.59%), with a mean of 2.3±1.1 concomitant medications per patient. Baseline laboratory parameters were all within normal ranges: ALT (28.5±8.2) U/L, AST (26.3±7.5) U/L, serum creatinine (82.4±15.6) μmol/L, fasting blood glucose (5.8±1.3) mmol/L, $CD4^+/CD8^+$ ratio (1.4±0.3) (Table 1), confirming no pre-existing organ or immune dysfunction that could confound ADR causality.

Laboratory baseline parameters

ALT (28.5±8.2) U/L, AST (26.3±7.5) U/L, serum creatinine (82.4±15.6) μmol/L, fasting blood glucose (5.8±1.3) mmol/L, $CD4^+/CD8^+$ ratio (1.4±0.3). Detailed baseline data are shown in Table 1.

Overall adverse reactions

Of 128 patients, 23 developed ADRs, with an overall mild ADR incidence of 17.97% (exposure-adjusted: 0.12 events per patient-day). No moderate or severe ADRs occurred. Symptoms were relieved with symptomatic treatment in 16 cases (69.57%) and resolved spontaneously after drug discontinuation in 7 cases (30.43%), with no treatment interruptions or adverse outcomes. This confirms the manageable safety of budesonide suspension nebulization in elderly patients in clinical practice.

By type of adverse reaction

Local ADRs were the main type (18 cases, 14.06%), accounting for 78.26% of all ADRs; systemic ADRs were rare (5 cases, 3.91%), accounting for 21.74% (Table 2). Oropharyngeal candidiasis (7 cases, 5.47%) was the most common local ADR, followed by hoarseness (6 cases, 4.69%) and throat irritation with cough (5 cases, 3.91%). Systemic ADRs included fatigue (2 cases, 1.56%), blood glucose fluctuation (1 case, 0.78%), rash (1 case, 0.78%) and headache (1 case, 0.78%). The single blood glucose fluctuation occurred in an elderly type 2 diabetes patient, reminding clinicians to pay close attention to blood glucose monitoring in this subgroup. Most local ADRs were associated with inadequate mouth rinsing, indicating a potential clinical link between rinsing compliance and local ADR risk.

Table 1: Patient baseline data (n, %,$\bar{x}$±s).

Baseline characteristics	N	Composition ratio (%)	Measurement data ($\bar{x}$±s)
Gender	-	-	-
Male	76	59.38	-
Female	52	40.62	-
Age grouping	-	-	-
60-79 years old	89	69.53	(68.72±5.31) years old
≥80 years old	39	30.47	(84.51±4.26) years old
BMI Grouping (kg/m²)	-	-	-
<24	70	54.69	(21.35±1.82)
≥24	58	45.31	(25.42±1.67)
Smoking history	-	-	-
Have	53	41.41	-
Not	75	58.59	-
Indications for medication	-	-	-
Bronchial asthma	45	35.16	-
Acute exacerbation of COPD	58	45.31	-
Acute exacerbation of chronic bronchitis	25	19.53	-
Number of underlying diseases	-	-	-
Not	12	9.38	-
1-2 types	56	43.75	-
≥3 types	60	46.87	-
Course of medication	-	-	-
≤14d	91	71.09	(7.82±2.35) d
>14d	37	28.91	(18.65±3.42) d
Mouthwash situation	-	-	-
Proper mouth rinsing	82	64.06	-
Improper mouth rinsing	46	35.94	-
Initial dose	-	-	-
1mg/time	85	66.41	-
2mg/time	43	33.59	-
Combined medication	-	-	(2.3±1.1) species
ALT（U/L）	-	-	(28.5±8.2)
AST（U/L）	-	-	(26.3±7.5)
Serum creatinine (μmol/L)	-	-	(82.4±15.6)
Fasting blood glucose (mmol/L)	-	-	(5.8±1.3)

Temporal distribution characteristics of adverse reactions

ADRs showed a mid-term high-incidence pattern, with the highest rate at 8–14 days (39.13%, 9/23), followed by early stage (≤7 days, 34.78%, 8/23) and late stage (>14 days, 26.09%, 6/23) (Table 3). Different ADR types had distinct temporal features: throat irritation with cough was mainly early-onset (80.00%, 4/5), while oropharyngeal candidiasis (57.14%, 4/7) and hoarseness (66.67%, 4/6) were concentrated in the 8–14 day window—consistent with the cumulative local immunosuppressive effect of budesonide. Kaplan–Meier analysis showed significantly earlier ADR onset in high-risk groups (≥80 years, treatment duration >14 days, inadequate mouth rinsing) (Log-rank χ^2=4.987, 5.892, 6.235, all p<0.05), suggesting the need for earlier ADR monitoring in these patients.

Univariate analysis of adverse reaction incidence

Univariate analysis identified 6 factors associated with ADR incidence (all p<0.05): age group, number of underlying diseases, treatment duration, mouth rinsing practice, $CD4^+/CD8^+$ ratio and concomitant medication types (Table 4). Gender, BMI, smoking history, medication indication, initial dose and baseline liver/renal function had no significant effects (all p > 0.05). Key clinical differences:ADR incidence was 28.21% in ≥80 years group vs. 13.48% in 60–79 years group;30.43% in the inadequate mouth rinsing group vs. 10.98% in standardized rinsing group;9.73% in the treatment duration >14 days group vs. 13.19% in ≤14 days group;25.00% in patients with ≥3 underlying diseases vs. 11.76% in those with <3 types.These differences highlight clinical factors that may increase ADR risk in elderly patients.

Table 2: Incidence of adverse reactions (cases, %).

Adverse reaction types	N	Incidence (%)	Severity (mild)	Handling method	Time of return (d)	Characteristics of the people involved
Local adverse reactions	18	14.06	18	-	-	-
Oropharyngeal candidiasis	7	5.47	7	Gargle with 2% sodium bicarbonate solution	3~5	Four cases were ≥80 years old, five cases did not rinse their mouths properly, and four cases had a treatment course >14 days.
Hoarse voice	6	4.69	6	Watermelon Frost lozenges	2~4	Three cases were ≥80 years old, four cases did not rinse their mouths properly, and three cases had a treatment course >14 days.
Throat irritation accompanied by cough	5	3.91	5	No special treatment required	1~3	Four patients were aged 60-79 years; two patients used standard mouthwash; and four patients had a treatment course of ≤14 days.
Systemic adverse reactions	5	3.91	5	-	-	-
fatigue	2	1.56	2	Rest + Enhanced Nutrition	2~3	Two patients were ≥80 years old, and two patients had ≥3 underlying diseases.
Blood sugar fluctuations	1	0.78	1	Adjusting the dosage of hypoglycemic drugs	4~6	One patient was ≥80 years old, one patient had diabetes, and one patient had a treatment course >14 days.
Rash	1	0.78	1	Discontinue medication + apply calamine lotion externally	3~5	One patient was aged 60-79 years, one patient had no underlying diseases, and one patient had a treatment course of ≤14 days.
Headache	1	0.78	1	No special treatment required	1~2	One patient was aged 60-79 years, one patient had hypertension, and one patient had a treatment course of ≤14 days.
Total	23	17.97	23	-	1~6	-

Table 3: Time-series distribution of adverse reactions (cases, %, $\bar{x}$±s).

Adverse reaction types	Early (≤7d) N (%)	Mid-term (8~14d) N (%)	Late (>14d) N (%)	Average time to occurrence (d)	Log-rank χ^2 value (vs. control group)	*p*
Oropharyngeal candidiasis	2 (28.57)	4 (57.14)	1 (14.29)	9.6±3.2	5.128	0.024
Hoarse voice	1 (16.67)	4 (66.67)	1 (16.67)	10.2±2.8	4.893	0.027
Throat irritation accompanied by cough	4 (80.00)	1 (20.00)	0 (0.00)	4.3±1.5	3.012	0.083
Fatigue	1 (50.00)	1 (50.00)	0 (0.00)	7.5±0.7	2.875	0.090
Blood sugar fluctuations	0 (0.00)	1 (100.00)	0 (0.00)	11.0±0.0	4.215	0.040
Rash	1 (100.00)	0 (0.00)	0 (0.00)	3.0±0.0	2.156	0.142
Headache	0 (0.00)	1 (100.00)	0 (0.00)	9.0±0.0	2.987	0.084
Total	8 (34.78)	9 (39.13)	6 (26.09)	8.8±3.5	-	-
Group comparison	-	-	-	-	-	-
Age ≥ 80 years old	3 (27.27)	5 (45.45)	3 (27.28)	7.6±3.1	4.987	0.026
Age group 60-79 years old	5 (41.67)	4 (33.33)	3 (25.00)	9.2±3.4	-	-
Group with a treatment course of >14 days	2 (18.18)	6 (54.55)	3 (27.27)	12.4±3.6	5.892	0.015
Group with a treatment course of ≤14 days	6 (50.00)	3 (25.00)	3 (25.00)	6.8±2.9	-	-
Non-standard mouthwash group	5 (35.71)	6 (42.86)	3 (21.43)	7.2±3.0	6.235	0.013
Standard mouthwash set	3 (33.33)	3 (33.33)	3 (33.34)	10.5±3.7	-	-

Table 4: Univariate analysis of adverse reactions (cases, %).

Influencing factors	N	Adverse reactions occurred (N, %)	No adverse reactions occurred (N, %)	χ^2/F	*p*
Gender	-	-	-	0.125	0.724
Male	76	14 (18.42)	62 (81.58)	-	-
Female	52	9 (17.31)	43 (82.69)	-	-
Age grouping	-	-	-	6.892	0.009
60-79 years old	89	12 (13.48)	77 (86.52)	-	-
≥80 years old	39	11 (28.21)	28 (71.79)	-	-
BMI Grouping（kg/m²）	-	-	-	0.346	0.556
<24	70	13 (18.57)	57 (81.43)	-	-
≥24	58	10 (17.24)	48 (82.76)	-	-
Smoking history	-	-	-	0.218	0.640
Have	53	10 (18.87)	43 (81.13)	-	-
Not	75	13 (17.33)	62 (82.67)	-	-
Indications for medication	-	-	-	1.235	0.539
Bronchial asthma	45	8 (17.78)	37 (82.22)	-	-
Acute exacerbation of COPD	58	11 (18.97)	47 (81.03)	-	-
Acute exacerbation of chronic bronchitis	25	4 (16.00)	21 (84.00)	-	-
Number of underlying diseases	-	-	-	7.652	0.006
<3 types	68	8 (11.76)	60 (88.24)	-	-
≥3 types	60	15 (25.00)	45 (75.00)	-	-
Course of medication	-	-	-	8.321	0.004
≤14d	91	12 (13.19)	79 (86.81)	-	-
>14d	37	11 (29.73)	26 (70.27)	-	-
Initial dose	-	-	-	0.568	0.451
1mg/time	85	15 (17.65)	70 (82.35)	-	-
2mg/time	43	8 (18.60)	35 (81.40)	-	-
Mouthwash situation	-	-	-	9.236	0.002
Proper mouth rinsing	82	9 (10.98)	73 (89.02)	-	-
Improper rinsing	46	14 (30.43)	32 (69.57)	-	-
Combined medication	-	-	-	4.562	0.033
<3 types	72	9 (12.50)	63 (87.50)	-	-
≥3 types	56	14 (25.00)	42 (75.00)	-	-
$CD4^+/CD8^+$ratio	-	-	-	5.128	0.024
≥1.2	96	14 (14.58)	82 (85.42)	-	-
<1.2	32	9 (28.12)	23 (71.88)	-	-
Baseline liver and kidney function levels (normal/abnormal)	-	-	-	0.892	0.345
Normal	105	18 (17.14)	87 (82.86)	-	-
Abnormal	23	5 (21.74)	18 (78.26)	-	-

Table 5: Multivariate logistic regression analysis of adverse reactions.

Variable	Regression coefficient (β)	Standard error (SE)	Wald	OR	95%CI	*p*
Age group (≥80 years old = 1)	1.177	0.542	4.752	3.245	1.123–9.376	0.030
Number of underlying diseases (≥3 = 1)	0.896	0.458	3.887	2.451	0.998–6.015	0.052
Course of medication (>14d=1)	1.064	0.536	3.965	2.897	1.012–8.294	0.048
Mouth rinsing status (not standardized = 1)	1.417	0.492	8.362	4.126	1.458–11.703	0.008
Combined medication types (≥3 types = 1)	0.757	0.432	3.065	2.135	0.897–5.056	0.087
$CD4^+/CD8^+$ratio (<1.2=1)	0.841	0.456	3.352	2.318	0.927–5.795	0.072
constant term	-1.782	0.345	26.891	0.167	0.082–0.340	<0.001

Table 6: Comparison of changes in laboratory indicators before and after medication ($\bar{x}$±s).

Laboratory indicators	Adverse reaction group (n=23)	No adverse reactions occurred in the group (n=105)	Differences between groups after medication (t, *p*)
fasting blood glucose (mmol/L)	Before medication: 5.9±1.3 After medication: 6.3±1.5	Before medication: 5.8±1.3 After medication: 5.9±1.2	t=1.256, *p*=0.211
ALT (U/L)	Before medication: 29.2±8.5 After medication: 30.5±9.1	Before medication: 28.3±8.1 After medication: 29.1±8.5	t=0.682, *p*=0.496
AST (U/L)	Before medication: 27.1±7.8 After medication: 28.3±8.2	Before medication: 26.1±7.4 After medication: 26.8±7.7	t=0.753, *p*=0.453
serum creatinine (μmol/L)	Before medication: 84.2±16.3 After medication: 85.7±17.1	Before medication: 82.1±15.4 After medication: 83.2±16.0	t=0.528, *p*=0.598
$CD4^+/CD8^+$ratio	Before medication: 1.3±0.3 After medication: 1.2±0.3	Before medication: 1.4±0.3 After medication: 1.4±0.3	t=1.892, *p*=0.060
White blood cell count ($\times10^9$/L)	Before medication: 6.5±1.2 After medication: 6.7±1.3	Before medication: 6.4±1.1 After medication: 6.5±1.2	t=0.897, *p*=0.371
Neutrophil ratio (%)	Before medication: 62.3±5.8 After medication: 63.5±6.2	Before medication: 61.8±5.6 After medication: 62.5±5.9	t=0.724, *p*=0.470

Multivariate logistic regression analysis of adverse reactions

Six variables with $p<0.05$ in univariate analysis were included in the multivariate logistic regression model, with additional adjustment for underlying respiratory diagnosis, disease severity and initial budesonide dose (Table 5). Three independent risk factors for ADRs were confirmed: Age ≥80 years (OR=3.245, 95% CI:1.123–9.376, *p*=0.030);Treatment duration >14 days (OR=2.897, 95% CI:1.012–8.294, *p*=0.048); Inadequate mouth rinsing (OR=4.126, 95% CI:1.458–11.703, *p*=0.008).Patients with ≥3 underlying diseases (OR=2.451, *p*=0.052), ≥3 concomitant medications (OR=2.135, *p*=0.087), or a $CD4^+/CD8^+$ ratio <1.2 (OR=2.318, *p*=0.072) had ORs >2.0, suggesting potential clinical risk that needs further verification in larger samples.

Analysis of changes in laboratory indicators

Post-medication laboratory indicators showed no statistically significant changes in either the ADR or non-ADR groups (all $p>0.05$), with no clinically meaningful abnormalities in liver/renal function, complete blood count, or immune function (Table 6). The ADR group had a slight increase in fasting blood glucose (5.9±1.3 to 6.3±1.5 mmol/L) and a minor decrease in $CD4^+/CD8^+$ ratio (1.3±0.3 to 1.2±0.3), but all values remained within normal ranges. No significant between-group differences were observed in the magnitude of indicator changes (all $p > 0.05$), confirming that budesonide nebulization has no obvious adverse effects on elderly patients' organ and immune function.

DISCUSSION

The results of this study showed that the overall incidence of adverse reactions to budesonide suspension via nebulization in elderly patients was 17.97%, all mild, with no serious adverse events, confirming that the overall safety of this drug in the elderly population is manageable. In terms of types of adverse reactions, local reactions accounted for as high as 78.26%, with oropharyngeal candidiasis (5.47%) and hoarseness (4.69%) as the main manifestations. This characteristic is closely related to budesonide's pharmacological properties.

Budesonide nebulized particles (≈15%-20% remaining in the oropharynx) exert local immunosuppressive effects by inhibiting oropharyngeal immune cell activation (Jin *et al*., 2025), which aligns with our study's finding that oropharyngeal candidiasis (5.47%) is the most common local ADR and inadequate mouth rinsing (a factor increasing oropharyngeal drug retention) is the strongest independent risk factor (OR=4.126) for ADRs (Xinchao and Hui, 2024). This immunosuppressive effect is amplified in the ≥80 years group (Xu *et al*., 2024), consistent with our data showing a 3.8-fold higher oropharyngeal candidiasis incidence in this subgroup (12.82%) compared with the 60-79 age group (3.37%). Budesonide-retained microparticles may penetrate submucosal tissue, stimulating vasodilation and inflammatory cell infiltration, which could contribute to the hoarseness and throat irritation observed in our study (4.69% and 3.91% incidence, respectively) (Xinyan and Zhenqiu , 2025). The study by Zhijun *et al*. (Zhijun *et al*.,2022) also confirmed that the incidence of local adverse reactions in elderly patients after ICS treatment was significantly higher than in middle-aged and young people, which cross-validates the results of this study.

The incidence of systemic adverse reactions was only 3.91%, mainly fatigue. Only one case of blood glucose fluctuation occurred and it was an elderly patient with type 2 diabetes. This result is attributed to budesonide's high first-pass hepatic metabolism (>90%), resulting in extremely low drug concentrations entering the

bloodstream and minimal impact on systemic metabolism (Resal *et al*., 2023). It is worth noting that for very elderly diabetic patients aged ≥80 years with treatment duration >14 days, it is necessary to monitor changes in blood glucose after medication to prevent excessively high blood glucose levels. This view is essentially the same as the conclusion of Gummlich *et al.* (Gummlich *et al.*,2022), who found that ICS may have a slight effect on blood glucose in diabetic patients.

This study found that the incidence of adverse reactions was highest in patients 8-14 days after medication, reaching 39.13%. Early adverse reactions mainly included throat irritation accompanied by cough, while mid-term adverse reactions were mainly manifested as oropharyngeal candidiasis and hoarseness. This temporal pattern is closely related to the cumulative "time-dose" effect of budesonide and the weakened mucosal repair capacity of elderly patients and this mid-term high-incidence characteristic is more prominent in high-risk groups such as the very elderly and those with inadequate mouth rinsing.

Throat irritation accompanied by cough occurred mostly in the early stage of treatment (80.00%), possibly due to direct stimulation of the airway mucosa by the drug. As the body gradually adapts, the symptoms usually subside spontaneously (Arun *et al*., 2025). The mid-term concentration of oropharyngeal candidiasis and hoarseness is a result of the cumulative local immunosuppressive effect of the drug: with short-term medication (≤7 days), mucosal damage can be compensated for by the body's own repair mechanisms. However, after 8-14 days of medication, the drug accumulates in the oropharynx, sufficient to trigger significant immunosuppression and the mucosal repair function gradually declines, leading to a high incidence of adverse reactions (Huahai , 2023). The clinical study by Jingjing *et al*. (Jingjing *et al*.,2026) also found that 12 weeks of ICS use was the peak period for local adverse reactions, consistent with the results of this study.

Kaplan-Meier time-to-event curve analysis showed that the onset of adverse reactions was significantly earlier in the non-standard mouthwash group, the group with a treatment course of >14 days and the group aged ⩾80 years, suggesting that these high-risk factors can accelerate the onset of adverse reactions. This finding clarifies the key time window for clinical ADR monitoring (8-14 days after medication) and provides a scientific basis for developing targeted and efficient monitoring programs.

That is, for high-risk groups, adverse reaction monitoring should be strengthened from the early stage of medication, especially in the middle stage, when oropharyngeal candidiasis and hoarseness should be investigated.

Multivariate logistic regression analysis identified age ≥80 years, treatment duration >14 days and failure to rinse the mouth properly as independent risk factors for adverse reactions, findings that are highly consistent with existing research and pharmacological mechanisms.This study, for the first time, quantifies the independent risk effects of these three factors in nebulized budesonide therapy for elderly patients and clarifies that inadequate mouth rinsing is the strongest modifiable risk factor, addressing a lack of quantitative clinical evidence in existing research.

Age ≥80 years (OR=3.245) is an important independent risk factor, reflecting the synergistic effect of physiological decline across multiple systems in the elderly. From a pharmacokinetic perspective supported by existing geriatric pharmacology research, budesonide is mainly metabolized by hepatic CYP3A4 and patients ≥80 years old have reduced CYP3A4 activity; this may potentially lead to prolonged drug elimination half-life and local drug accumulation, which aligns with our study's finding that age ≥80 years is an independent risk factor for ADRs (OR=3.245) (Xueyang W *et al*., 2025).In this study, the incidence of adverse reactions in patients aged ≥80 years (28.21%) was 2.1 times that of the 60-79 year old group (13.48%) and the incidence of oropharyngeal candidiasis (12.82%) was 3.8 times that of the younger group (3.37%), which directly reflects the cumulative effect of the drug. From a pharmacodynamic perspective, thymic atrophy in elderly patients leads to an imbalance of T lymphocyte subsets, a decreased $CD4^+/CD8^+$ ratio and a decline in immune function, making them more sensitive to the immunosuppressive effect of budesonide (Qin C, 2025), further increasing the risk of infectious adverse reactions. Honghua *et al*. (Honghua *et al*., 2025) also found, in their study, that budesonide use was the most important risk factor for adverse reactions in patients over 80 years of age, a conclusion that is essentially the same as that of this study.

Treatment duration >14 days (OR=2.897) reflects the cumulative time outcome of budesonide adverse reactions. Airway inflammatory diseases in the elderly often exhibit chronic and persistent characteristics, necessitating long-term medication. However, long-term use can disrupt the balance between therapeutic efficacy and mucosal protection (Yimin *et al*., 2025). When the treatment period is less than 14 days, airway mucosal damage can be balanced through self-repair mechanisms. However, when the treatment period exceeds 14 days, this balance is lost, leading to progressive decline in mucosal barrier function (Sungho *et al*., 2025). Furthermore, the drug inhibits the phagocytic function of neutrophils and macrophages, resulting in long-term colonization and proliferation of opportunistic pathogens such as Candida albicans in the oropharynx (Mengqi *et al*., 2025). In this

study, the incidence of adverse reactions was highest during the 8-14 day treatment period, further supporting the clinical recommendation that the course of ICS treatment for acute exacerbations of COPD in the elderly, especially the very elderly, should not exceed 14 days.

Inadequate gargling, the highest independent risk factor (OR=4.126), primarily exacerbates the residue and accumulation of budesonide in the oropharynx (Min *et al*., 2025). After nebulized inhalation, approximately 15%–20% of budesonide particles deposit in the oropharynx. Proper gargling can remove over 80% of the residual drug (Expert Consensus on Rational Drug Use in Nebulized Inhalation Therapy (2024 Edition)) (Clinical Pharmacy Branch of Chinese Medical Association *et al*., 2024). However, in those who do not gargle properly, the residual drug forms a "persistent focus of action" in the oropharynx. On the one hand, this prolongs the contact time between the drug and the mucosa, enhancing both immunosuppressive and stimulatory effects (Bhanwra *et al*., 2024); on the other hand, drug residue alters the pH of the oropharynx, creating an acidic environment conducive to Candida albicans proliferation (Jingjing *et al*., 2026).This study provides direct quantitative clinical evidence to support making standardized mouth rinsing a mandatory nursing measure for nebulized budesonide therapy in elderly patients, especially the very elderly.

Furthermore, univariate analysis showed that patients with ≥3 underlying diseases, ≥3 concurrent medications and a $CD4^+/CD8^+$ ratio <1.2 had a significantly higher incidence of adverse reactions. Although these patients did not enter the final multivariate model, their odds ratios (ORs) were all >2.0, suggesting a potential risk association. Elderly patients with multiple underlying diseases often have diabetes, hypertension, etc. The hyperglycemic environment in diabetic patients inhibits neutrophil chemotaxis and phagocytic function, thereby synergistically enhancing the immunosuppressive effect of budesonide (Mian *et al*., 2024). Some antihypertensive drugs (such as amlodipine) and hypoglycemic drugs (such as gliclazide) may inhibit CYP3A4 activity, slow down budesonide metabolism and indirectly increase the risk of drug accumulation (Cheng *et al*., 2025). A $CD4^+/CD8^+$ ratio <1.2 reflects a weakened immune function and reduced resistance to infection, which may also increase the risk of adverse reactions. Since the sample sizes of these subgroups in this study were relatively small, this may have reduced statistical power. Further multicenter, large-sample prospective studies are needed to verify the potential risks associated with these factors in the very elderly population aged ≥80 years.

This study is based on the three critical knowledge gaps in existing budesonide safety research for the elderly population proposed in the introduction and its core scientific contributions and novelties are reflected in three key aspects, which make up for the deficiencies of previous studies and advance the current understanding of budesonide safety in elderly patients with inflammatory airway diseases:

Existing studies mostly treat elderly patients (≥60 years) as a single homogeneous group and lack targeted safety evidence for the very elderly population with more severe physiological decline. This study stratified the elderly population into 60-79 years and ≥80 years for the first time and found that the ADR incidence in the very elderly (28.21%) was 2.1 times that of the 60-79 age group (13.48%) and the incidence of oropharyngeal candidiasis (12.82%) was 3.8 times that of the younger elderly group. We further quantified the independent risk effect of age ≥80 years (OR=3.245, p=0.030) through multivariate logistic regression, providing quantitative and targeted safety data for the very elderly—a population with the most severe physiological decline and the highest clinical medication demand. This finding fills a gap in stratified safety research on budesonide for the elderly and provides a direct scientific basis for precision medication in the very elderly.

Previous studies reported only the overall incidence of budesonide ADRs in the elderly, without examining the temporal distribution and onset characteristics of different types of ADRs. This study first found that budesonide ADRs in the elderly show a "mid-term high-incidence" characteristic, with the highest incidence (39.13%) occurring 8-14 days after medication; different types of ADRs have distinct temporal onset patterns: throat irritation and cough are mainly early-onset (≤7 days), while oropharyngeal candidiasis and hoarseness (the main local ADRs) are mainly mid-term-onset (8-14 days). Kaplan-Meier time-series analysis further confirmed that high-risk factors (inadequate mouth rinsing, treatment duration >14 days, age ≥80 years) can accelerate the occurrence of ADRs. This finding clarifies the key time window for clinical ADR monitoring (8-14 days after medication). It provides a scientific basis for developing targeted, efficient clinical monitoring programs, replacing the traditional, all-round monitoring mode in clinical practice with focused monitoring of mid-term local ADRs in high-risk groups, greatly improving the efficiency of clinical ADR monitoring and nursing.

Although inadequate mouth rinsing is generally considered a potential risk factor for ICS-related local ADRs, existing research lacks clinical quantitative evidence to confirm its independent risk effect and specific risk weight in nebulized budesonide therapy for the elderly. This study found that inadequate mouth rinsing is the strongest independent risk factor for budesonide ADRs in the elderly (OR=4.126, p=0.008), with an ADR incidence of 30.43% in the inadequate mouth rinsing group, 2.8 times that of the standardized mouth rinsing group (10.98%). This finding quantitatively confirms the causal relationship between inadequate

mouth rinsing and budesonide ADRs in the elderly population and identifies a key modifiable clinical factor for ADR prevention. Unlike non-modifiable factors such as advanced age and physiological decline, standardized mouth rinsing is an easy-to-implement, low-cost and high-efficiency nursing measure in clinical practice; this study provides strong and direct clinical evidence for making standardized mouth rinsing a mandatory nursing procedure for nebulized budesonide therapy in the elderly and has important practical significance for reducing the risk of ADRs through simple clinical nursing intervention.

In addition, this study provides targeted safety data for budesonide suspension of a specific specification (2ml:1mg) produced by Sichuan Prite Pharmaceutical Co., Ltd., which is commonly used in primary clinical practice in China, filling the gap in safety research of this specific drug and providing a direct reference for primary clinical medication. This study has the following limitations: (1) This single-center retrospective study with a small sample size (n=128) has inherent selection bias; the included patients are from a single hospital's geriatric psychiatry department, limiting the extrapolation of conclusions. (2) Inconsistent medical record documentation among staff introduced information bias in ADR identification and reduced the accuracy of WHO-UMC causality assessment; mild ADRs may be underreported, which directly affects the reliability of ADR statistics. (3) Therapeutic drug monitoring (TDM) was not conducted, making it impossible to directly quantify blood drug concentrations and local tissue drug concentrations and lacking direct evidence for the association between pharmacokinetics and adverse reactions. (4) Objective efficacy indicators such as pulmonary function and inflammatory factors were not included in the observation indicators, making it impossible to analyze the balance between efficacy and safety and also failing to follow up on the long-term prognosis of adverse reactions. (5) The influence of human factors such as patients' cognitive function and medication adherence on the occurrence and outcome of adverse reactions was not considered. Future multi-center prospective studies with larger samples are needed to reduce these biases and verify the study results.

CONCLUSION

The overall incidence of adverse reactions to budesonide suspension via nebulized inhalation in elderly patients with inflammatory airway diseases was 17.97%, mainly mild local reactions and the overall safety was manageable in this real-world cohort. This study systematically clarifies the distinct temporal distribution pattern of budesonide ADRs in the elderly (with a mid-term high incidence at 8–14 days after medication) and identifies three independent risk factors for ADRs, among which inadequate mouth rinsing is a key modifiable clinical factor—a finding that provides real-world observational evidence for optimizing the clinical use of this drug in elderly patients. This study also provides stratified safety evidence and quantitative risk data for the very elderly (≥80 years), confirming that they have a significantly higher ADR risk in clinical practice and suggesting the need for more precise, individualized medication and monitoring strategies for this subgroup in routine clinical care. Based on the observational findings of this study, it is reasonable to propose tentative clinical practice considerations for the high-risk factors identified: for the very elderly patients (≥80 years old), it may be prudent to consider low-dose, short-course dosing regimens in combination with enhanced monitoring of drug metabolism-related indicators and clinical symptoms; the duration of treatment should be strictly evaluated on an individual basis, with timely dose reduction after symptom relief during acute exacerbations to avoid unnecessary extension of treatment beyond 14 days; clinical attention should be paid to the key monitoring time window (8–14 days after medication) and close clinical observation of local ADRs such as oropharyngeal candidiasis and hoarseness is recommended for high-risk groups; standardized mouth rinsing is a clinically feasible and low-cost intervention that may help reduce the risk of local ADRs and it is suggested to develop personalized guidance plans based on the cognitive and mobility abilities of elderly patients to improve adherence to this nursing measure. Given the retrospective, observational nature of this study, these clinical considerations are exploratory and require validation through further prospective, interventional studies. Future research should conduct multi-center, large-sample prospective studies, combining therapeutic drug monitoring and inflammatory factor detection to further refine the individualized dosing regimen of budesonide suspension for the stratified elderly population, especially the very elderly aged ≥80 years and provide more comprehensive evidence-based support for the safe and effective use of inhaled corticosteroids in elderly patients with inflammatory airway diseases.

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Weifeng Meng: Responsible for writing for this research; Lingfei Fu: Responsible for data processing; Hui Huang: Responsible for conceptualization and translation. All the authors have read and approved the final version for publication.

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Data availability statement
The datasets generated during and/or analysed during the

current research are available from the corresponding author on request.

Ethical approval

This retrospective study has obtained formal ethical approval from the Medical Ethics Committee of Shaoxing Seventh People's Hospital (Approval Number: SXQYRYY-2025-106). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data

https://pjps.pk/uploads/2026/08/SUP1787226754.pdf

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