Healthcare resource consumption prior to asthma-related death: a nationwide descriptive study

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Abstract

Background: Although asthma mortality declined sharply until the mid-2000s, a stagnation in mortality has been observed over the past decade in different countries.

Objective: The objective of this study is to describe healthcare resource consumption for patients who died from asthma in France.

Method: This study was conducted using data from the French National Health Data System. Patients who died from asthma between 2013 and 2017 were identified by the ICD10 codes J45 and J46. Health care consumption data were collected. Patients were categorized into four categories according to age: ≧75, (18–75), (12–18), (0–12). Daily doses of ICS were categorized according to GINA guidelines.

Results: A total of 3829 patients were included. No ICS or an inadequate ICS dose was observed in 43.8%, 50.6%, 48.1%, and 54.0% of patients aged ≧75, (18–74), (12–18), and (0–12) years, respectively. Dispensation of six or more SABA canisters was observed in 37.2%, 49.0%, and 70.3% of patients aged of ≧75, (18–75), and (12–18) years, respectively. Omalizumab dispensation rate was very low [1.1% and 2.8% in patients aged ≧75 and (18–75) years]. The proportion of patients with a pulmonologist office visit was 13.8% and 14.6% in patients ≧75 and (18–75) years, respectively. A lung function test was noted in only 18.6%, 28.3%, and 25.9% of patients ≧75, (18–75) and (12–18) years, respectively.

Conclusion: Half of the patients who died from asthma received inadequate ICS doses and only a small proportion had access to biological therapies. Less than 15% were referred to a specialist.

Keywords: asthma, death, inhaled steroids, consumption

Introduction

Asthma is a chronic respiratory disease that affects 340 million people worldwide. Although asthma mortality declined sharply until the mid-2000s, it would appear that mortality rate has been stagnating for several years. The number of deaths from asthma has not changed significantly over the last two decades in England. In a recent study, only a 2.5% reduction in asthma deaths was observed in England and Wales from 2001 to 2017. In the United Kingdom, an increase of 7.7% was observed between 2017 and 2018. In the United States, asthma deaths slightly decreased (3.3%) between 2001 and 2009. Multiple factors have a detrimental impact on asthma mortality. In the 2014 UK National Review of Asthma Deaths, preventable factors were identified in two-thirds of the medical records of 197 patients who died from asthma. In this study, overall asthma management (acute and chronic) was satisfactory in only 16% of these patients, and in only 4% of the children and young people. The authors highlighted that...
Asthma treatment was not appropriate due to over-dispensing of short-acting reliever inhalers (SABA) and insufficient provision of inhaled corticosteroid (ICS). In a study conducted on Swedish national registries, overuse of SABA was also associated with an increased risk of exacerbation and asthma-related death. In those studies, no data on the use of biological therapies are available.

The risk factors of inappropriate management in asthma mortality highlight that care pathway improvement is highly warranted in asthma patients in order to decrease asthma mortality. However, little is known about care pathway in these patients. In a literature review of asthma management, a reliable and effective coordination between health professionals appears to be crucial in asthma management. Referrals for specialist care (pulmonologist and pediatrician) seem to be low in asthma patients prior to death. However, the care pathway for patients who died from asthma, particularly specialist referrals, has not been extensively studied and could help to develop strategies to reduce asthma mortality. Large epidemiological studies on asthma mortality are highly needed.

Our study aims to describe the healthcare resource consumption of patients who died from asthma between 2013 and 2017 in France. For this purpose, we used the French national health insurance database (SNDS).

**Population and methods**

**Data sources**

A prospective observational study was conducted using the SNDS database, which integrates the main French health databases (French health insurance inter-scheme information system, hospital data, and death registry). In France, health consumption data in the SNDS are collected from patients covered by mandatory health insurance (about 99% of the French population). The SNDS database provides a global overview of patients’ care pathway without any loss to follow-up for several years in France. The data available in the SNDS database are as follows: age, gender, health status, cause of death, place of residence, the use of reimbursed outpatient care (drug dispensation, medical consultations, and medical and biological procedures), and the use of hospital care (reason for hospitalizations, care facility, and expensive drugs). Patients with asthma can benefit from long-term illness (LTI) coverage, which provides full reimbursement of asthma-related healthcare costs by health insurance. This information is also available in the SNDS. A high dose of maintenance inhaled therapies, daily symptoms, frequent nocturnal asthma symptoms, frequent exacerbations, physical activity depending on symptoms, and FEV1 or peak expiratory flow (PEF) < 60% of predicted values, or PEF variability > 30% are requested for LTI full coverage. A connection between healthcare resources and the national registry of death has been established since 2013 (Supplementary Figure 1).

**Inclusion criteria**

Patients who died from asthma between 2013 and 2017 were identified according to the ICD-10 (International Classification of Diseases: 10th Revision) codes, J45 and J46, recorded in the national register of death as the main cause of death for that period. Duplicate patients and patients with no health consumption 2 years prior to death were excluded.

**Ethical approval**

The study protocol was approved by the French national ethics committee (registration no. TPS 578472). The protocol was also approved by the French Data Protection Authority (registration no. 919303v1).
CCI score. Updated weights are also applied for better assessment of the CCI.

Healthcare resource consumption. SABA use was quantified as the number of canisters recorded within the past 12 months before death. To enable a comparison of different types and number of doses in the SABA canisters, a standardized SABA canister unit was defined as 150 doses. Patients were grouped by the number of SABA canisters recorded: ≤2 (considered appropriate use), (3–5), (6–10), and ≥11.11

ICS use included both monotherapy and fixed combinations within the last 12 months prior to death. The mean daily ICS dose (in budesonide equivalents) was defined according to GINA guidelines.18 In children aged 0 to 11 years, daily ICS dose was categorized into low dose (100–200 μg), medium dose (201–400 μg), and high dose (>400 μg) (Supplementary Table 1). In teenagers (12–17 years old) and adults (≥18 years old), daily ICS dose was categorized into low dose (200–400 μg), medium dose (401–800 μg) and high dose (>800 μg). A very low daily dose was defined as a dose inferior to the lower limit of a low daily dose that cannot be considered as maintenance therapy. The number of patients with ICS/LABA (long acting beta agonists) dispensation within the last 12 months prior to death and the number of patients treated with omalizumab within the last 12 months prior to death was described. No other biological therapies were evaluated because omalizumab was the only biological therapy commercialized during the study period. The cumulative dose of oral steroids within 12 months was expressed as prednisone equivalence. Flu and pneumococcal vaccine dispensation were recorded.

Emergency room visits and hospitalizations for asthma within 12 months prior to death were recorded. The number of outpatient consultations with a pulmonologist, pediatrician, and/or general practitioner (GP) and the proportion of patients with at least one outpatient consultation with a pulmonologist, pediatrician, ear-nose-throat specialists (ENT), or a GP within the 12 months prior to death were determined. Reimbursement for complete blood count, skin prick tests, specific IgE quantification, lung function tests, computed tomography (CT) scan, bronchial endoscopy, and nocturnal polygraphy were also recorded.

Statistical analysis
A descriptive analysis of patients’ characteristics was performed. Qualitative variables were expressed in numbers and percentages. Quantitative variables were expressed as mean and standard deviations or median and interquartile range (IQR) when relevant. In order to explain the link between asthma mortality and healthcare consumption, correlations between the density of GP or pulmonologist and the number of asthma-related deaths within the department or region (territorial administrative division in France) were assessed and compared using Pearson’s correlation coefficient and test, respectively. Statistical analyses were performed using SAS Enterprise Guide software, version 7.15 HF8.

Results

Patients’ characteristics
From 1 January 2013 to 31 December 2017, 3863 subjects were recorded with a leading cause of death related to asthma in the cause-of-death registry (the proportion of patients with other main causes of death is indicated in Supplementary Table 2). The study flowchart is presented in Figure 1. After exclusion of duplicate patients and patients with no health consumption 2 years prior to death, 3829 patients were included in the final analysis. The vast majority of subjects included were adults (n = 3765, 98.3%) and predominantly female (n = 2584; 67.5%; Table 1).

For all categories of age, the proportion of patients with LTI full coverage ranges from 11.1% to 23.1%.

Death characteristics
Home was the main place of death (55.6%) for adult patients less than 75 years old, whereas the other patients mainly died at the hospital or in a nursing home (Table 2). However, a death at home was also observed between 18.5% and 28.5%, in the other age categories. Asthma death seasonality was clearly observed in patients aged ≥75 years with excess mortality during winter (Supplementary Figure 2).

Asthma treatment
The proportion of patients with no ICS dispensation ranged from 18.5% and 37.7% according to age categories (Table 3). If we considered
patients with no ICS dispensation or very low ICS dose, the proportion increased with a range from 43.8% to 54.0%. In addition, a high daily dose of ICS was observed in a minority of patients (from 14.8% to 32.8% according to age). It is remarkable to note that 81.5% and 73.0% of children aged of 12–17 and 0–12 had at least one dispensation of ICS, whereas only 33.3% and 26.2% had moderate to high daily dose of ICS, respectively (Table 3). Regarding the ICS/LABA combination, almost half of patients had at least one dispensation within 12 months prior to death.

A majority of patients had two or more SABA canister dispensations within the last 12 months prior to death. The proportion of teenagers and children aged <12 with two or more SABA canister dispensation within the last 12 months prior to death was 92.6% and 81.1%, respectively. A dispensation of six SABA canisters or more within the last 12 months was observed in 37.2% and 49.0% of adults aged ≥75 and 18–74 years, respectively. Regarding systemic steroid dispensation, a majority of patients had at least one dispensation. The median dose of systemic steroid was over 1 g for patients over 11 years old. The dispensation of biological therapies was very low in our cohort because only 1.1% and 2.8% received omalizumab among patients aged ≥75 and 18–74, respectively.

Other drugs of interest
The proportion of patients with a dispensation of influenza or pneumococcal vaccine was low particularly among teenagers (14.8% and 7.4% in this group, respectively) (Supplementary Table 3). Dispensation of anxiolytics, hypnotics, and antidepressants was high among adults. The proportion of patients with antidepressant was quite similar to the general population because approximately one-third of the French population takes antipsychotic medication.19

Hospitalizations, ED visits, and outpatient visits
A vast majority of patients had a GP office visit within the last 12 months prior to death (Table 4). However, the proportion of patients with a pulmonologist office visit was very low in all age categories (13.8% and 14.6% in adults ≥75 and 18–74 years, respectively). The proportion of patients with at least one GP, pulmonologist, or ENT office visit remained stable over time (Table 5). No correlation was observed between the density of GP or pulmonologist and the number of asthma death (Supplementary Table 4). Lung function test reimbursement was noted in less than 30% regardless of age. The reimbursements for other tests are presented in Supplementary Table 5. The proportion of patients with pulmonologist office visits or lung function tests
among those having no-or-very-low ICS use or overuse of SABA is indicated in Supplementary Table 6. The proportion of patients with at least one emergency department (ED) visit within 12 months prior to death ranged from 22.9% to 48.1% according to age (Table 4). A history of at least one hospitalization for asthma within the last 12 months prior to death was infrequent because less than 20% experience hospitalization for asthma within 12 months prior to death.

Discussion
This study is one of the largest studies on patients who died from asthma, and the first one to use the exhaustive French health database to do so. In our study, half of the study population received no ICS or a dose that is not compatible with maintenance therapy. It is well described that regular use of inhaled steroids is associated with a decreased risk of asthma-related death and the premature cessation of ICS can hasten death.8,20,21 In the 2014 UK National Review of
Asthma Deaths, insufficient provision of inhaled corticosteroid medication was one of the key avoidable factors involved in asthma mortality. The fact that inadequate doses were noted in our study means either that the patient did not continue the maintenance therapies prescribed by a physician or that physicians discontinue treatment prematurely. Although our study was not designed to assess the reasons for inadequate ICS dose, we hypothesize that non-adherence was probably the main factor of very low ICS use.

In our study, despite a high ICS dose within the last 12 months prior to death, 32.8% and 27.5% of patients aged ≥75 and (18–75) died from asthma. Given the high dose of ICS, those patients could be eligible for biological therapies. However, omalizumab dispensation ranged from only 1.1%–2.8% in adults. It is surprising to note that omalizumab dispensation was very low, whereas more than a quarter of the patients had a high ICS dose. Between 2013 and 2017, omalizumab was the only biological therapy available in severe asthma. The low dispensation of omalizumab in patients who died from asthma could be explained by the fact that patients may not have been eligible for this therapy (i.e. for allergic asthma). However, we have no access to biological data in the SNDS database. Consequently, we cannot know the asthma phenotype to confirm our hypothesis. The underutilization of omalizumab in patients with a high ICS dose has been shown in a study conducted in Germany and Italy. Moreover, in a cohort of severe asthma, it was estimated that 31% to 41% were eligible for omalizumab, which corroborates the underutilization of biological therapies in our study. According to the very low proportion of patients with total IgE quantification, we hypothesize that the underutilization of omalizumab is not due to non-eligibility of patients with non-allergic asthma but a lack of referral for the prescription of biological therapies.

The underutilization of ICS and omalizumab is probably due to the inadequate specialist care referrals in our study. In fact, less than 15% of the patients who died from asthma were referred to a pulmonologist within the last 12 months prior to death. In a study performed in the United Kingdom between 2006 and 2017, the percentage of the high-risk group of asthma patients referred for specialist care was less than 20%. An evaluation of asthma deaths in the United Kingdom found that 20% of the deaths investigated were related to avoidable factors associated with referrals.

It is also surprising to observe that less than 30% of the adults who died from asthma had lung function tests within the last 12 months prior to death. A lack of spirometry use has been described in patients with suspected chronic airway inflammatory diseases in primary care. Our description of the proportion of patients with lung function tests who died from asthma is the first. Lung function tests are considered to be a central tool in asthma evaluation and are highly recommended in asthma diagnosis and follow-up. In France, the use of spirometry in primary care is still very limited.

**Table 2. Place of death for patients who died from asthma between 2013 and 2017 in France according to age.**

| Characteristics | Age ∈ (75; +) (N = 2571) | Age ∈ (18–75) (N = 1194) | Age ∈ (12–18) (N = 27) | Age ∈ (0;12) (N = 37) |
|-----------------|--------------------------|--------------------------|------------------------|-----------------------|
| Place of death, n (%) | | | | |
| Home | 735 (28.5) | 664 (55.6) | 5 (18.5) | 10 (27.0) |
| Hospital | 1112 (43.2) | 394 (32.9) | 16 (59.2) | 22 (59.5) |
| Nursing home | 624 (24.3) | 20 (1.7) | – | – |
| Public space | 8 (0.3) | 44 (3.7) | 1 (3.7) | 2 (5.4) |
| Other, unspecified or missing information | 92 (3.6) | 72 (6.0) | 5 (18.5) | 3 (8.1) |
Table 3. Description of asthma therapy dispensations within the last 12 months prior to death in patients who died from asthma between 2013 and 2017 in France according to age.

| Age  | At least one ICS dispensation, a n (%) | Daily ICS dose, b µg Median (IQR) ° | No ICS or inadequate dose | Low | Medium | High | ICS/LABA dispensation, n (%) | Including the following daily ICS dose inadequate dose | Low | Medium | High | Dispensation of 2 or more SABA canisters, n (%) | Number of SABA canisters, median (IQR) ° | Number of SABA canisters recorded, n (%) | Systemic steroid dispensation b,c |
|------|--------------------------------------|-------------------------------------|---------------------------|-----|--------|------|-----------------------------|-----------------------------------------------|-----|--------|------|-----------------------------------------------|-------------------------------|----------------------------------|-----------------------------|
|      | (N = 2571)                           |                                     |                           |     |        |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |
| Age  | N (%)                                |                                      |                           |     |        |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |
| ∈ (75;+)| 1692 (65.8)                         | 744 (62.3)                           | 22 (81.5)                 | 27 (73.0) |       |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |
| ∈ (18–75)| 795.5 (394.2–7095.9)                | 699 (262.8–1353.5)                  | 350.4 (168.6–591.3)      | 135.7 (65.7.5–2893.1) |       |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |
| ∈ (12–18)| 844 (32.8)                          | 328 (27.5)                           | 4 (14.8)                  | 6 (16.2) |       |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |
| ∈ (0;12)| 390 (15.2)                          | 156 (13.1)                           | 5 (18.5)                  | 4 (10.8) |       |      |                             |                                               |     |        |      |                                                              |                               |                                  |                             |

ICS, inhaled corticosteroids; LABA, long acting beta agonists; IQR, interquartile range; SABA, short-acting reliever inhalers.

aICS or ICS/LABA.
bDaily dose of ICS is expressed in budesonide equivalence.
cSystemic steroid dose is expressed in prednisone equivalence.
A history of ED visits or hospitalization for asthma is recognized as one of the main factors associated with asthma mortality. It has been shown that more than one hospital admission for asthma, three ED visits or five physician visits increased the asthma mortality risk substantially and exponentially. In our study, a minority of patients who died from asthma had at least 1 ED visit or hospitalization prior to death. This highlights the fact that a history of an ED visit or hospitalization should be taken into account for asthma evaluation. However, physicians who are in charge of asthma patients should bear in mind that asthma-related death can occur even with no history of ED visit or hospitalization.

This study has limitations. Like in many others studies on this topic, asthma diagnosis was based on ICD-10 J45 and J46 codes. These codes were based on data available on death certificates. Consequently, there is a risk of misdiagnosis. However, it has been shown that using death...
certificates to identify asthma-related deaths has a specificity of 99%. This was confirmed in a recent study in which asthma-related death had a good correlation with ICD-10 codes based on death certificates. However, we think that elderly people who presumably died of asthma should be as much the focus of interest as young people. In fact, elderly people with asthma have an excess in the risk of death compared to elderly people with no asthma. This is why we decided to keep people older than 75 in our analysis. In order to provide accurate data, we categorized our cohort into four groups according to age.

**Conclusion**

Half of the patients who died from asthma had an inadequate ICS dose and only a small proportion had access to biological therapies in France. Less than 15% were referred to a specialist and less than 30% had lung function tests. SABA dispensation was high, particularly in teenagers. Given that a minority of patients were referred to a specialist, we estimate that the recent approval of biological therapies will not have a substantial impact on asthma mortality. Prescription of an adequate ICS dose, avoidance of premature discontinuation of ICS, education programs and referral to a specialist should be the focus of interest in order to achieve a significant reduction in asthma mortality. Those data will be further updated in order to analyze the effect of the recent approval of biological therapies on asthma mortality.

**Declarations**

*Ethics approval and consent to participate*

The study protocol was approved by the French national ethics committee (registration no. TPS 578472). The protocol was also approved by the

| Table 5. Percentage of patients with at least one GP, pulmonologist, or ear-nose-throat specialist (ENT) office visit within the last 24 months prior to death. |
|---|---|---|---|
| Age | Period of time (months prior to death) | GP office visit | Pulmonologist office visit | ENT office visit |
| [0; 12] | [6; 0] | 94.59 | 2.70 | 8.11 |
| | [12; 6] | 75.68 | 0.00 | 5.41 |
| | [18; 12] | 70.27 | 0.00 | 5.41 |
| | [24; 18] | 75.68 | 0.00 | 8.11 |
| [12; 18] | [6; 0] | 81.48 | 7.41 | 0.00 |
| | [12; 6] | 77.78 | 0.00 | 0.00 |
| | [18; 12] | 74.07 | 3.70 | 3.70 |
| | [24; 18] | 85.19 | 3.70 | 0.00 |
| [18; 75] | [6; 0] | 86.93 | 9.55 | 2.01 |
| | [12; 6] | 84.42 | 8.21 | 1.76 |
| | [18; 12] | 84.76 | 6.78 | 2.09 |
| | [24; 18] | 82.83 | 7.20 | 2.18 |
| [75; + ] | [6; 0] | 87.51 | 8.83 | 1.79 |
| | [12; 6] | 87.36 | 8.67 | 2.64 |
| | [18; 12] | 88.37 | 7.70 | 2.26 |
| | [24; 18] | 88.88 | 7.12 | 2.61 |

ENT, ear-nose-throat specialist; GP, general practitioner.
French Data Protection Authority (registration no. 919303v1).

Consent for publication
Not applicable.

Author contributions
Laurent Guilleminault: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Availability of data and materials
The data are the property of the national health insurance and cannot be divulged or shared.

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Supplemental material
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