No Harmful Effects of Steroids in Severe Exacerbations of COPD Associated With Influenza

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Abstract

**Background:** COPD has large impact on patient morbidity and mortality worldwide. Acute exacerbations (AECOPD) are mostly triggered by respiratory infections including influenza. While corticosteroids are strongly recommended in AECOPD, they are potentially harmful during influenza. We aimed to evaluate if steroid treatment for AECOPD due to influenza may worsen outcomes.

**Methods:** A retrospective analysis of a Swiss nationwide hospitalisation database was conducted identifying all AECOPD hospitalisations between 2012 and 2017. In separate analyses, outcomes concerning length-of-stay (LOS), in-hospital mortality, rehospitalisation rate, admission to intensive care unit (ICU), empyema and aspergillosis were compared between AECOPD during and outside influenza season; AECOPD with and without laboratory confirmed influenza; and AECOPD plus pneumonia with and without laboratory confirmed influenza.

**Results:** Patients hospitalised for AECOPD during influenza season showed shorter LOS and fewer ICU admissions but higher rehospitalisation rates compared to those hospitalised outside influenza season. Patients with confirmed influenza infection had lower in-hospital mortality and rehospitalisation rates but higher risk for ICU admission than those without confirmed influenza. In patients with AECOPD plus pneumonia, there was a higher risk of ICU admission for those with laboratory-confirmed influenza compared to those without.

**Conclusions:** Using different indicators for influenza as the likely cause of AECOPD, we found no consistent evidence of worse outcomes of AECOPD due to influenza. Assuming that most of these patients received corticosteroids, as it is accepted standard of care throughout Switzerland, this study provides important information and supports the current practice of using corticosteroids for AECOPD independent of the influenza status.

**Background**

Chronic obstructive pulmonary disease (COPD) with its still growing number of patients and high mortality ranks among the top five causes of death worldwide[1–3]. Due to its chronicity, COPD patients often need lifelong therapy. Especially acute exacerbations of COPD (AECOPD) make the disease accountable for a high burden for the health care system and economy [4, 5].

AECOPD are estimated to be caused in 75% of cases by respiratory infections, of which about one third are each bacterial, viral or bacterial/viral coinfections [6]. Among the viral aetiologies, the influenza virus, which is treatable, is estimated to trigger about 5–10% of AECOPD [7, 8]. Therefore, testing for influenza is recommended for all patients with AECOPD and symptoms suspicious for influenza, especially during influenza season [9, 10]. If influenza is detected, it is usually considered as the likely trigger of an AECOPD.
Basic pillars for the treatment of patients with AECOPD are short-acting bronchodilators, treatment of the underlying infection, sufficient oxygenation and systemic corticosteroids[11]. In a systematic Cochrane review, the latter were shown to result in better outcomes for lung function, symptoms, length of hospital stay (LOS) and treatment failure in AECOPD compared to placebo[12].

With accumulating data since the 2009 Swine flu pandemic, corticosteroids have fallen out of favour as adjunctive therapy in the management of influenza as they were associated with an increased mortality [13]. Controversy still exists about the use of corticosteroids in patients with pneumonia without COPD [14–17]. The German S3 guidelines recommend against systemic corticosteroids in patients with severe influenza pneumonia who do not suffer from COPD [18]. However, the same guidelines state that COPD patients with increasing obstruction in the context of pneumonia should receive systemic corticosteroids as adjunctive therapy [18]. One study suggested that asthmatics had a less severe outcome than non-asthmatics from Influenza A/H1N1 2009 possibly due to corticosteroid use who were found to benefit from systemic corticosteroids for respiratory stabilization[19].

In short, the strong recommendation for the use of corticosteroids for AECOPD and the current recommendation of not using corticosteroids in influenza still represent a discrepancy for the treatment of exacerbations of COPD with confirmed or suspected influenza. Given the lack of RCTs, we performed this retrospective analysis to bring more light into the surprisingly little investigated field of treatment of AECOPD in combination with influenza infection.

**Methods**

As data source, we used the “Swiss Hospital Database” provided by the Swiss Federal Office for Statistics (FOS), which is a nation-wide dataset and belongs to the FOS[20]. This database provides a diagnosis list including one main diagnosis plus up to 50 additional diagnoses following the ICD-10 system for each hospitalisation in Switzerland since 1998. It therefore provides an accurate representation of the (hospitalised) Swiss population and has previously been used for similar analyses[21].

The hospitalization data set used in this analysis was provided by the Swiss Federal Office for Statistics. In this database, the patient information is fully anonymized. Thereby, and in accordance with relevant guidelines and regulations, no written informed consent is necessary for patients, since they are unidentifiable due to the anonymization. As a consequence, the protocol did not have to be approved by an institutional committee.

**Inclusion/exclusion criteria**

We included data from 2012 to 2017, as professional and consistent coding of diseases started only in 2012, when coded diagnoses became revenue-relevant for hospitals and assurers. The only additional exclusion criterion was patient age of < 40 years, as COPD can formally hardly be diagnosed below that limit.
Analyses and statistical methods

After screening the about eight million database entries between 2012 and 2017 with the statistical program R, Vienna, we conducted three separate analyses working with ICD-10-coded diagnoses such as AECOPD, influenza, pneumonia and their possible combinations. Relevant codes and code-combinations to build the comparison groups for the three analyses were elaborated together with the coding department of the Cantonal Hospital St. Gallen. As the coding order results from the relative weighing of each diagnosis in hospitalizations with several occurring medical problems, all hospitalisation-related diagnoses were screened. For each separate analysis conducted, differences between groups concerning LOS, in-hospital mortality and risk of rehospitalisation for AECOPD within the study period (2012–2017), were assessed. In addition, we assessed the risk of ICU admission and aspergillosis in each group and, for analysis 3 only, the occurrence of empyema.

Analysis 1 compared outcomes of patients with AECOPD during vs. outside the influenza epidemic period. Because of the fundamental difference in treatment approach, all patients with pneumonia were excluded. Influenza epidemic period was defined using information provided by the Swiss general practitioners-led surveillance tool “Sentinella”, which defines for each influenza epidemic the calendar weeks during which a threshold of a predefined number of consultations per 100’000 inhabitants with suspected influenza is surpassed, thereby defining the national epidemic period ([www.sentinella.ch](http://www.sentinella.ch))[22]. As the Swiss Hospital Database classifies data in a month-based system, influenza epidemic weeks of the “Sentinella” system were translated into influenza epidemic months. Each month containing at least one day of an influenza epidemic week was declared as influenza epidemic month.

Analysis 2 compared AECOPD with laboratory proof of concomitant influenza infection with AECOPD without proof of concomitant influenza infection, i.e. influenza PCR was either negative or not conducted. Due to fundamental difference in management, all patients with pneumonia were preliminary excluded.

Analysis 3 compared AECOPD with and without concomitant laboratory-confirmed influenza infection, among patients with an additional diagnosis of pneumonia.

Differences in terms of LOS were tested using Wilcoxon rank sum tests. The proportions of in-hospital mortality and the re-hospitalisation rate as well as the additional outcomes were compared between groups using Pearson’s Chi-squared test for count data. The associated effect estimates (mean differences and odds-ratios) are given together with their associated 95% confidence interval.

Results

In analysis 1 (Table 1) we compared 26’616 episodes of AECOPD during influenza seasons with 42’442 episodes of AECOPD outside of influenza seasons.
Table 1
Clinical outcomes of patients with AECOPD hospitalised during and outside the influenza season

| Variable                        | AECOPD during influenza season | AECOPD outside influenza season | OR/MD                  | p        |
|---------------------------------|--------------------------------|--------------------------------|------------------------|----------|
| Cases, n                        | 26'616                         | 42'442                         |                        |          |
| Female, %                       | 46                             | 45                             | OR: 1.02               | 0.209    |
|                                 |                                |                                | (95% CI: 0.99–1.05)    |          |
| **Outcomes**                    |                                |                                |                        |          |
| Mean LOS, days                  | 11.3                           | 11.6                           | MD: -0.29              | < 0.001  |
|                                 |                                |                                | (95% CI: -0.45– -0.12) |          |
| In-hospital mortality, %        | 5.6                            | 5.4                            | OR: 1.05               | 0.190    |
|                                 |                                |                                | (95% CI: 0.98–1.12)    |          |
| Risk of re-hospitalization, %   | 33                             | 31                             | OR: 1.13               | < 0.001  |
|                                 |                                |                                | (95% CI: 1.09–1.17)    |          |
| ICU admission, %                | 13.4                           | 14.0                           | OR: 0.95               | 0.028    |
|                                 |                                |                                | (95% CI: 0.91–0.99)    |          |
| Aspergilloss, %                 | 0.1                            | 0.2                            | OR: 0.71               | 0.091    |
|                                 |                                |                                | (95% CI: 0.47–1.06)    |          |

OR: odds ratio; MD: mean difference; p: p-value; CI: confidence interval

For hospitalisations with AECOPD during the influenza season, the LOS was significantly shorter (11.3d vs. 11.6d, \( p < 0.001 \)), there was no significant difference in terms of in-hospital mortality (5.6% vs. 5.4%, \( p = 0.190 \)), the risk of being re-hospitalised for AECOPD was higher (33% vs. 31%, \( p < 0.001 \)), risk for ICU admission was lower (13.4% vs. 14.0%, \( p = 0.028 \)), while there was no significant difference in the occurrence of aspergillosis (0.1% vs.0.2%, \( p = 0.091 \)).

In analysis 2 (Table 2) we compared 1004 AECOPD episodes with laboratory-confirmed influenza infection with 67'688 AECOPD episodes without laboratory-confirmed influenza.
Table 2
Clinical outcomes of patients with AECOPD with and without confirmed influenza diagnosis

| Variable                              | AECOPD with influenza | AECOPD without influenza | OR/MD       | p       |
|---------------------------------------|-----------------------|--------------------------|-------------|---------|
| Cases, n                              | 1'004                 | 67'688                   |             |         |
| Female, %                             | 46                    | 45                       | OR: 1.05    | 0.443   |
|                                       |                       |                          | (95% CI: 0.93–1.19) |         |
| Outcomes                              |                       |                          |             |         |
| Mean LOS, days                        | 10.9d                 | 11.5d                    | MD: -0.62   | 0.162   |
|                                       |                       |                          | (95% CI: -1.48–0.25) |         |
| In-hospital mortality, %              | 3.3                   | 5.5                      | OR: 0.58    | 0.003   |
|                                       |                       |                          | (95% CI: 0.40–0.82) |         |
| Risk of re-hospitalization, %         | 29                    | 37                       | OR: 0.72    | <0.001  |
|                                       |                       |                          | (95% CI: 0.62–0.82) |         |
| ICU admission, %                      | 16                    | 14                       | OR: 1.23    | 0.016   |
|                                       |                       |                          | (95% CI: 1.04–1.46) |         |
| Aspergillosis, %                      | 0.2                   | 0.2                      | OR: 1.15    | 0.694   |
|                                       |                       |                          | (95% CI: 0.14–4.27) |         |

OR: odds ratio; MD: mean difference; p: p-value; CI: confidence interval

For patients with AECOPD and influenza, LOS was not different (10.9d vs. 11.5d, p = 0.162), in-hospital mortality (3.3% vs. 5.5%, p = 0.003) as well as re-hospitalisation rate for AECOPD (29% vs. 37%, p < 0.001) were lower, risk of ICU admission was higher (16% vs 14%, p = 0.016), while there were no significant differences for aspergillosis (0.2% vs. 0.2%, p = 0.694).

In analysis 3 (Table 3) we compared 734 AECOPD episodes with pneumonia and confirmed influenza with 29'971 AECOPD episodes with pneumonia without influenza diagnosis.
Table 3
Clinical outcomes of patients with AECOPD and pneumonia with and without influenza diagnosis

| Variable                        | AECOPD with pneumonia with influenza | AECOPD with pneumonia without influenza | OR/MD                          | p       |
|---------------------------------|--------------------------------------|----------------------------------------|---------------------------------|---------|
| Cases, n                        | 734                                  | 29,971                                 | OR: 1.11 (95% CI: 0.95–1.29)    | 0.206   |
| Female, %                       | 39                                   | 36                                     | OR: 1.11 (95% CI: 0.95–1.29)    | 0.206   |
| **Outcomes**                    |                                      |                                        |                                 |         |
| Mean LOS, days                  | 14.5                                 | 13.9                                   | MD: 0.65 (95% CI: -0.43–1.73)   | 0.234   |
| In-hospital mortality, %        | 7.4                                  | 8.6                                    | OR: 0.84 (95% CI: 0.62–1.11)    | 0.257   |
| Risk of re-hospitalization, %   | 34                                   | 34                                     | OR: 1.00 (95% CI: 0.85–1.17)    | 0.969   |
| ICU admission, %                | 29                                   | 21                                     | OR: 1.55 (95% CI: 1.31–1.82)    | < 0.001 |
| Aspergillosis, %                | 0.8                                  | 0.4                                    | OR: 2.05 (95% CI: 0.74–4.62)    | 0.129   |
| Empyema, %                      | 0.7                                  | 0.9                                    | OR: 0.74 (95% CI: 0.24–1.74)    | 0.627   |

OR: odds ratio; MD: mean difference; p: p-value; CI: confidence interval

For patients with AECOPD with pneumonia and influenza, LOS (14.5d vs. 13.9d, p = 0.234), in-hospital mortality (7.4% vs. 8.6%, p = 0.257) and re-hospitalisation rate for AECOPD (34% vs. 34%, p = 0.969) were not different, the risk of ICU admission was higher (29% vs. 21%, p < 0.001), while aspergillosis (0.8% vs. 0.4%, p = 0.129) and empyema (0.7% vs. 0.9%, p = 0.627) were not significantly different.

**Discussion**

Our study, which analysed all nationwide AECOPD hospitalisations from 2012 to 2017 using 3 separate analyses, resulted in three main findings: First, AECOPD during influenza seasons did not have worse
outcomes than outside influenza seasons, with shorter LOS and ICU admission but similar mortality and only slightly increased risk of rehospitalisation. Second, outcome was better if influenza was detected during hospitalisation for AECOPD than if not, with lower mortality and risk of rehospitalisation, similar LOS and only slightly increased risk of ICU admission. Third, in patients with AECOPD and pneumonia, influenza diagnosis was associated with increased risk of ICU admission but no significant difference in any other outcome. Complications in form of aspergillosis were rare and not higher in any of our subgroups. Overall, these data confirm that the clinical outcome of AECOPD in Switzerland was not affected by likely or confirmed influenza diagnosis thereby supporting the safety of the current management including corticosteroids.

Clinicians in Swiss hospitals usually adhere to local guidelines or practices which are typically based on recommendations of the Centers for Disease Control and Prevention or European Centre for Disease Prevention and Control to determine when and in what patients influenza testing should be done, but there are no countrywide directives with general validity. Therefore, in common clinical practice, testing for influenza virus infection outside the influenza epidemic period in patients without major suspicion for influenza is rarely performed. As a result, AECOPD with influenza may be considerably underdiagnosed – especially outside influenza epidemic period - and subsequently erroneously diagnosed and coded as AECOPD without influenza infection. Because of their simplicity, relatively low costs and fast results, during influenza epidemic rapid influenza diagnostic tests (RIDTs) are still a widely used method for influenza testing [10][23]. As RIDTs show a high specificity, but a lower sensitivity compared to real-time polymerase chain reaction (RT-PCR) testing or the newer rapid molecular assays, many cases of influenza infections as triggers for AECOPD may have been missed as they were classified as (false) negative results[24]. For these reasons, we performed separate analyses: The first analysis comparing AECOPD during vs. outside the influenza season likely included most influenza episodes but was not very specific as there still are many other infectious and non-infectious causes for exacerbation even during influenza periods, particularly for patients vaccinated against influenza. This analysis showed discordant results with no difference in in-hospital mortality, a significantly shorter LOS but slightly higher risk of rehospitalisation for patients admitted during influenza season. An increased awareness for respiratory symptoms of COPD patients during influenza season might have led to lower threshold to hospitalise them in case of suspicion for influenza-caused exacerbation and therefore quicker initiation of appropriate treatment including antivirals with faster clinical response[25], even though we did not have access to medication data. This might also explain the significantly higher rate of rehospitalisations for AECOPD and the lower need for ICU admission during influenza periods. The hypothesis of lower hospitalisation-threshold and therefore better outcomes during influenza season mirrors the results of a study on asthmatic and non-asthmatic patients with influenza, where earlier hospital admission and the early use of corticosteroids – both associated with asthmatics – were found as an explanation for better outcomes compared to hospitalised non-asthmatics[19]. Earlier hospitalisation together with generally higher hospital occupancy during winter and spring resulted in greater pressure to discharge patients, and might have been at least partially responsible for the observed shorter mean LOS during influenza periods.
In contrast, comparing outcomes for AECOPD in patients with versus without influenza diagnosis in the second analysis would be most specific for influenza but miss many episodes likely caused by influenza[26]. There was a slightly increased risk of ICU admission but no significant difference in terms of LOS, while in-hospital mortality and rehospitalisation rates were significantly lower in patients with influenza. This supports the notion that corticosteroids, which we assume were also given in AECOPD with influenza coinfection and in the slightly more frequently occurring ICU settings of influenza positive patients, did not worsen the outcome of those exacerbations, even though the use of steroids had shown a negative impact as adjunctive treatment in influenza alone[13][27]. Consistent with this, we recently showed that COPD patients had less pneumonia-related complications, which possibly may be due to their use of inhaled corticosteroids[28]. These results confirm previous data from Korea and Hong Kong, that severity and outcomes were similar between AECOPD with or without viral detection [29, 30]. In contrast, older data suggested that there was a larger drop in peak flow and a longer recovery time in patients with viral AECOPD [25]. This might be confounded by the observation that viral exacerbations were more frequent in patients with higher GOLD stages [31]. A recent Canadian study showed that among 4755 patients with COPD hospitalised during influenza seasons, those with influenza diagnosis had significantly higher rates of mechanical ventilation, ICU admission and mortality than influenza test-negative patients.[32]

Finally, the special situation of patients who had an exacerbation of COPD with pneumonia - for which there is a German guideline recommendation [18] - was analysed by comparing outcomes between those with influenza diagnosis and those without. Here we also found an increased risk of ICU admission but no significant differences in any other outcome, which supports the current recommendation for corticosteroids if an AECOPD occurs simultaneously with an influenza infection. Of note is the low number of cases (637 hospitalisations in five years) in the influenza test-positive group and the high percentage of ICU admissions in both groups. No significant differences between groups in terms of complications such as aspergillosis or empyema were detected in our nationwide study which is also reassuring.

In general, our study did not find consistent evidence of a worse outcome in patients with AECOPD and any of our surrogates of influenza infection (epidemic period, laboratory-confirmed diagnosis) compared to patients without those surrogates. Of note, in all three analyses, there was one outcome (either risk of re-hospitalisation or risk of ICU admission) which was worse in the presumed influenza group, however other parameters and most importantly mortality were either not different or in favour of the presumed influenza group. If we assume in the absence of medication data in this database, that Swiss patients with AECOPD are generally - and in accordance with the 2020 GOLD report and current recommendations [33] - treated with corticosteroids, irrespective of a diagnosis of influenza or the respiratory season, our data supports the safety of corticosteroids in the majority of patients with AECOPD including those due to influenza. Even though influenza virus replication is increased in the presence of corticosteroids [34] and was shown in a recent meta-analysis to result in higher mortality and more nosocomial infections in influenza-associated severe pneumonia and acute-respiratory distress syndrome [35], these effects were not present in the population of patients with COPD in our study. As possible explanation we hypothesize
that chronically obstructed lungs react differently and the major clinical determinants in this situation are rather the obstruction and inflammation[36], which are reduced with corticosteroids, rather than the viral cytopathic effect of influenza, which would be exacerbated by corticosteroids. However, the exact reasons for these observed differences between patients with and without COPD are not well understood.

**Limitations**

While the retrospective nationwide study design allowed to analyse a large number of hospitalisations, it has limitations as all retrospective studies including detection bias.

By using coding data, our study is dependent on coding quality. Coding errors such as carrying over an exacerbation from a former hospitalisation in patients with stable COPD might have resulted in erroneous inclusions or exclusions of hospitalisations. Nevertheless, to code and bill a diagnosis, a criterion of related work-up or clinical evidence has to be present, and as coding of hospitalisation data became revenue-relevant for the stationary healthcare service providers in Switzerland in 2012, it is performed by professional coders ensuring high coding quality. Still, as a result of being a fairly young domain, coding may still be in a process of consolidation and have undergone slight changes throughout the period of our study.

Another weakness of our study was the lack of baseline characteristics (e.g. exact age or smoking status) in the dataset.

The main weakness is the lack of medication data in the database. With this, we can only make assumptions on how frequently corticosteroids are used in AECOPD in general and in particular when influenza is diagnosed or suspected. Nevertheless, as for hospitalised patients with AECOPD the use of systemic steroids is standard of care in Switzerland and we are confident that most patients received them.

The main strength of this study is the size of the dataset which includes data from all hospitalisations in Switzerland and provided more than eight million entries of hospitalisations from 2012 to 2017 thereby avoiding selection bias. This made it possible – in contrast to other study designs, which extrapolate from a random sample to the entire population – to accurately assess the total amount of hospitalisation cases in Switzerland. This resulted in more than 30’000 cases for the smallest analysis and almost 70’000 for the bigger ones, what lies beyond most clinical trials and supports the robustness of our observations.

**Conclusions**

Using different comparisons and indicators for influenza as a cause of AECOPD, this study did not find evidence of a worse outcome in patients with AECOPD due to influenza. Assuming that most patients with AECOPD received corticosteroids as it is accepted standard of care throughout Switzerland, this study provides important information and supports the safety of the current practice of routine
corticosteroid treatment in patients with AECOPD, also in the setting of likely influenza. Further studies including actual medication data would be needed to confirm this current practice.

List Of Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| COPD         | Chronic obstructive pulmonary disease |
| AECOPD       | Acute exacerbation of COPD |
| LOS          | Length of stay |
| ICU          | Intensive care unit |
| FOS          | Federal Office for Statistics |
| RCT          | Randomised controlled trial |
| ICD – 10     | International Classification of Diseases - 10 |
| RIDT         | Rapid influenza diagnostic test |
| RT-PCR       | Real-time polymerase chain reaction |

Declarations

Ethics approval and consent to participate

As all patient information is anonymised, patients are unidentifiable and no written consent was necessary.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the Swiss Federal Office for Statistics but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Swiss Federal Office for Statistics.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

S.S. and W.A. wrote the main manuscript text and prepared the figures. F.B. carried out the statistical calculations and analyzes. F.R., F.W. and M.B. added valuable inputs and improvements to the manuscript. All authors have contributed substantially to this manuscript, have read and agreed with the submitted version and have no potential conflicts of interest to disclose.

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