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No evidence of harmful effects of steroids in severe exacerbations of COPD associated with influenza

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Abstract

Purpose 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 nation-wide hospitalization 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, 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 hospitalized for AECOPD during influenza season showed shorter LOS (11.3 vs. 11.6 day, $p < 0.001$) but higher rehospitalisation rates (33 vs 31%, $p < 0.001$) compared to those hospitalized outside influenza season. Patients with confirmed influenza infection had lower in-hospital mortality (3.3 vs. 5.5%, $p = 0.010$) and rehospitalisation rates (29 vs. 37%, $p < 0.001$) than those without confirmed influenza.

Conclusion Using different indicators for influenza as the likely cause of AECOPD, we found no consistent evidence of worse outcomes of AECOPD due to influenza for hospitalized patients. Assuming that most of these patients received corticosteroids, as it is accepted standard of care in Switzerland, this study gives no evidence to change the current practice of using corticosteroids for hospitalized AECOPD independent of the influenza status.

Keywords COPD · Influenza · AECOPD · Corticosteroids

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

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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 favor 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 corticosteroids used for maintenance therapy [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 management dilemma for the treatment of exacerbations of COPD with confirmed or suspected influenza. Given the lack of RCTs, we performed this retrospective analysis to shed more light into this surprisingly little investigated topic.

Methods

As data source, we used the "Swiss Hospital Database" provided by the Swiss Federal Statistical Office (FSO), which is a nation-wide dataset and belongs to the FSO [20]. This database provides a diagnosis list including one main diagnosis plus up to 50 additional diagnoses following the ICD-10 system for each hospitalization in Switzerland since 1998. It therefore provides an accurate representation of the (hospitalized) Swiss population and has previously been used for similar analyses [21]. The diagnoses are listed as provided by the hospitals which usually engage dedicated coding experts who extract information from available medical records.

In this database, provided by the Swiss FSO, 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. The database contains very limited epidemiologic information and largely lacks clinical details such as severity of disease, smoking history or vaccination status.

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 8 million database entries between 2012 and 2017 with the statistical program R, 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 hospitalisations with several occurring medical problems, all hospitalization-related diagnoses were screened. For each separate analysis conducted, differences between groups concerning LOS, in-hospital mortality and risk of re-hospitalization for AECOPD within the study period (2012–2017) were assessed. In addition, we assessed the risk of 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. 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) [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 1 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 polymerase chain reaction (PCR) was either negative or not conducted. Due to fundamental difference in management, all patients with pneumonia were preliminary excluded from analyses 1 and 2.

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

The exact ICD-10 codes used to construct the comparison groups for analysis 1 to 3 are available in the supplementary material.

Differences in terms of LOS were tested using Wilcoxon rank sum tests. The proportions of in-hospital mortality and

the re-hospitalization 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. Mean differences and odds ratios were adjusted for gender and age category (in 5 year increments).

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.

For hospitalisations with AECOPD during the influenza season, the LOS was significantly shorter (11.3 vs. 11.6 day, $p < 0.001$), there was no significant difference in terms of in-hospital mortality (5.6 vs. 5.4%, $p = 0.751$), and the risk of being re-hospitalized for AECOPD was higher (33 vs. 31%, $p < 0.001$), while there was no significant difference in the occurrence of aspergillosis (0.1 vs. 0.2%, $p = 0.289$).

In analysis 2 (Table 2), we compared 1004 AECOPD episodes with laboratory-confirmed influenza infection with 67,688 AECOPD episodes without laboratory-confirmed influenza.

For patients with AECOPD and lab-confirmed influenza, LOS (10.9 vs. 11.5 days, $p = 0.083$) and risk for aspergillosis (0.2 vs. 0.2%, $p = 0.998$) were not different, but in-hospital mortality (3.3 vs. 5.5%, $p = 0.010$) as well as re-hospitalization rate for AECOPD (29 vs. 37%, $p < 0.001$) were lower.

In analysis 3 (Table 3), we compared among COPD patients, 734 episodes with pneumonia and confirmed influenza with 29,971 episodes with pneumonia without influenza diagnosis.

For COPD patients with a pneumonia episode with and without influenza, LOS (14.5 vs. 13.9 days, $p = 0.226$), in-hospital mortality (7.4 vs. 8.6%, $p = 0.679$), re-hospitalization rate for AECOPD (34 vs. 34%, $p = 0.999$) risk of aspergillosis (0.8 vs. 0.4%, $p = 0.322$) and empyema (0.7 vs. 0.9%, $p = 0.815$) were not significantly different.

Table 1 Clinical outcomes of patients with AECOPD hospitalized during and outside influenza season

Variable	AECOPD during influenza season	AECOPD outside influenza season	OR/MD	p
Cases, n	26,616	42,442		
Age distribution	n (%)	n (%)		< 0.001
40–44 years	131 (0.5)	285 (0.7)		
45–49 years	433 (1.6)	711 (1.7)		
50–54 years	868 (3.3)	1512 (3.6)		
55–59 years	1666 (6.3)	2831 (6.7)		
60–64 years	2619 (9.8)	4219 (9.9)		
65–69 years	3823 (14.4)	6098 (14.4)		
70–74 years	4592 (17.3)	7619 (18.0)		
75–79 years	4700 (17.7)	7347 (17.3)		
80–84 years	4242 (15.9)	6588 (15.5)		
85–89 years	2586 (9.7)	3827 (9.0)		
90–94 years	819 (3.1)	1247 (2.9)		
95 + years	137 (0.5)	158 (0.4)		
Female, %	46	45	OR: 1.02 (95% CI 0.99–1.05)	0.209
Outcomes				
Mean LOS, days	11.3	11.6	Adj. MD: − 0.31 (95% CI: − 0.48 to − 0.14)	< 0.001
In-hospital mortality, %	5.6	5.4	Adj. OR: 1.03 (95% CI 0.96–1.10)	0.751
Risk of re-hospitalization, %	33	31	Adj. OR: 1.13 (95% CI 1.10–1.17)	< 0.001
Aspergillosis, %	0.1	0.2	Adj. OR 0.72 (95% CI 0.49–1.07)	0.289

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

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	1004	67,688		
Age distribution	n (%)	n (%)		0.859
40–44 years	6 (0.6)	408 (0.6)		
45–49 years	20 (2.0)	1120 (1.7)		
50–54 years	38 (3.8)	2328 (3.4)		
55–59 years	61 (6.1)	4415 (6.5)		
60–64 years	97 (9.7)	6703 (9.9)		
65–69 years	145 (14.4)	9723 (14.4)		
70–74 years	197 (19.6)	11,954 (17.7)		
75–79 years	171 (17.0)	11,809 (17.4)		
80–84 years	159 (15.8)	10,613 (15.7)		
85–89 years	81 (8.1)	6297 (9.3)		
90–94 years	26 (2.6)	2028 (3.0)		
95 + years	3 (0.3)	290 (0.4)		
Female, %	46	45	OR: 1.05 (95% CI 0.93–1.19)	0.443
Outcomes				
Mean LOS, days	10.9	11.5	Adj. MD: − 0.61 (95% CI − 1.29 to 0.08)	0.083
In-hospital mortality, %	3.3	5.5	Adj. OR: 0.59 (95% CI 0.42–0.84)	0.01
Risk of re-hospitalization, %	29	37	Adj. OR: 0.71 (95% CI 0.62–0.89)	< 0.001
Aspergillosis, %	0.2	0.2	Adj. OR: 1.13 (95% CI 0.28–4.58)	0.998

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

Discussion

Our study, which analyzed all nation-wide AECOPD hospitalisations from 2012 to 2017 using three separate analyses, resulted in three main findings: First, AECOPD during influenza seasons did not have worse outcomes than outside influenza seasons, with shorter LOS but similar mortality and only slightly increased risk of re-hospitalization. Second, outcome was better if influenza was detected during hospitalization for AECOPD than if not, with lower mortality and risk of rehospitalisation at similar LOS. Third, in COPD patients with pneumonia, influenza diagnosis was associated with no significant difference in any outcome. Complications in form of aspergillosis were rare and not higher in any of our sub-groups. Overall, based on these data, there is no evidence of harmful effects on the clinical outcome of AECOPD in Switzerland by likely or confirmed influenza diagnosis, which is important information regarding the current management including corticosteroids [23].

Clinicians in Swiss hospitals usually adhere to local guidelines or practices, 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, what leads to the widespread use of PCR or antigen testing during influenza epidemic period [24]. In contrast, 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, 25]. As RIDTs show a high specificity, but a lower sensitivity compared to real-time (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 [26]. 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—rather a sensitivity analysis—as

Table 3 Clinical outcomes in COPD patients of episodes of pneumonia with and without influenza diagnosis

Variable	Pneumonia with influenza in patients with COPD	Pneumonia without influenza in patients with COPD	OR/MD	p
Cases, n	734	29,971		
Age distribution	n (%)	n (%)		0.015
40–44 years	4 (0.5)	142 (0.5)		
45–49 years	19 (2.6)	396 (1.3)		
50–54 years	25 (3.4)	770 (2.6)		
55–59 years	38 (5.2)	1494 (5.0)		
60–64 years	69 (9.4)	2554 (8.5)		
65–69 years	100 (13.6)	4027 (13.4)		
70–74 years	139 (18.9)	5168 (17.2)		
75–79 years	120 (16.3)	5567 (18.6)		
80–84 years	107 (14.6)	5147 (17.2)		
85–89 years	68 (9.3)	3338 (11.1)		
90–94 years	40 (5.4)	1183 (3.9)		
95 + years	5 (0.7)	185 (0.6)		
Female, %	39	36	OR: 1.11 (95% CI 0.95–1.29)	0.206
Outcomes				
Mean LOS, days	14.5	13.9	Adj. MD: 0.65 (95% CI: -0.41 to 1.71)	0.226
In-hospital mortality, %	7.4	8.6	Adj. OR: 0.86 (95% CI 0.65–1.14)	0.679
Risk of re-hospitalization, %	34	34	Adj. OR: 1.00 (95% CI 0.86–1.17)	0.999
Aspergillosis, %	0.8	0.4	Adj. OR: 1.94 (95% CI 0.85–4.42)	0.322
Empyema, %	0.7	0.9	Adj. OR: 0.69 (95% CI 0.28–1.68)	0.815

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

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 for hospitalization in case of suspicion for influenza-caused exacerbation and, therefore, quicker initiation of appropriate treatment including antivirals with faster clinical response [27]. Unfortunately, we did not have access to medication data. This might also explain the significantly higher rate of re-hospitalisations for AECOPD during influenza periods. The hypothesis of lower hospitalization 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 hospitalized non-asthmatics [19]. Earlier hospitalization together with generally higher hospital occupancy during winter and spring results 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 likely misses many episodes caused by influenza [28]. There was no significant difference in terms of LOS, while in-hospital mortality and re-hospitalization 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, did not worsen the outcome of those exacerbations, in contrast to their negative impact as adjunctive treatment in influenza alone [13, 29]. 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 [30]. These

results confirm previous data from Korea and Hong Kong, that severity and outcomes were similar between AECOPD with or without viral detection [31, 32]. In contrast, older data suggested that there was a larger drop in peak flow and a longer recovery time in patients with viral AECOPD [27]. This might be confounded by the observation that viral exacerbations were more frequent in patients with higher GOLD stages [33]. A recent Canadian study showed that among 4755 patients with COPD hospitalized during influenza seasons, those with influenza diagnosis had significantly higher rates of mechanical ventilation, ICU admission, and mortality than influenza test-negative patients [34]. A further possible explanation for the result might be that hospitals with better standard of care are more consequent at influenza testing.

Finally, the special situation of COPD patients with a pneumonia episode—for which there is a German guideline recommendation—was analyzed by comparing outcomes between those with influenza diagnosis and those without [18]. Here, we did not find significant differences in any of the outcomes, which supports the current recommendation for corticosteroids in these patients. Of note is the low number of cases in the influenza test-positive group (734 hospitalisations with influenza vs. 29,971 without in 5 years). We assume that there is a substantial underdiagnosis of influenza-positive cases, which weakens the significance of this analysis. Still, our first two analyses point into the same direction. Furthermore, no significant differences between those groups in terms of complications such as aspergillosis or empyema were detected, 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. In all three analyses, there was only one outcome—risk of re-hospitalization—in analysis 1, which was worse in the presumed influenza group, while other parameters and most importantly mortality were either not different or in favor of the presumed influenza group.

Unfortunately, we did not have access to medication data to ultimately prove our associations. Still, we can assume that Swiss patients with AECOPD generally and in accordance with the 2020 GOLD report and current recommendations are treated with corticosteroids, irrespective of a possible or confirmed diagnosis of influenza [35] for the following reasons. First, the generally good adherence to guidelines in management of AECOPD. Second, in case of suspected AECOPD, corticosteroid treatment is usually initiated empirically and shortly after hospital admission, while the result of influenza testing, if performed at all, is usually not available yet. Third, an influenza diagnosis was confirmed in only a minority of likely influenza-associated AECOPD episodes, which only would have possibly raised the concern about withholding corticosteroids.

Using an administrative database, it is impossible to exclude that a few patients may have been only subsequently coded as AECOPD and, therefore, may not have initially received corticosteroids. However, we do not consider this frequent enough of an event to have distorted our results.

Therefore, our data rather support 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 [36] 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 [37], these effects were not present in the population of patients with COPD in our study. Indeed, a recent meta-analysis of corticosteroids for ARDS indicated a survival benefit for ARDS of any etiology [38]. 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 [39], 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 nation-wide study design allowed to analyze a large number of hospitalisations, it has limitations as all retrospective studies including detection bias. Using coding data, our study is dependent on coding quality. Coding errors 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 hospitalization 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., details regarding means of COPD diagnosis or distinction from alternative diagnoses such as asthma, exact age, severity of disease or smoking or influenza vaccination status), which are not available in the dataset. For this reason, we could only adjust our analyses for gender and age category (in 5 year increments). As the analysis was restricted to hospitalized patients, we cannot generalize our findings to ambulatory patients.

The main weakness is the lack of medication data in the database. With this, we can only make assumptions on how frequently corticosteroids as well as other medication (e.g., oseltamivir) are used in AECOPD in general and in particular when influenza is diagnosed or suspected. Nevertheless, as for hospitalized 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 8 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 hospitalization 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 showed no evidence of harmful effects of the current practice of routine corticosteroid treatment in patients hospitalized with AECOPD, also in the setting of likely influenza. Nevertheless, due to the lack of explicit information about the administered medication, final confirmation can only be obtained through prospective and ideally randomized controlled trials.

Declarations

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