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)[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 (95% CI: 0.99–1.05)	0.209
Outcomes				
Mean LOS, days	11.3	11.6	MD: -0.29 (95% CI: -0.45 – -0.12)	< 0.001
In-hospital mortality, %	5.6	5.4	OR: 1.05 (95% CI: 0.98–1.12)	0.190
Risk of re-hospitalization, %	33	31	OR: 1.13 (95% CI: 1.09–1.17)	< 0.001
ICU admission, %	13.4	14.0	OR: 0.95 (95% CI: 0.91–0.99)	0.028
Aspergillosis, %	0.1	0.2	OR: 0.71 (95% CI: 0.47–1.06)	0.091

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 (95% CI: 0.93–1.19)	0.443
Outcomes				
Mean LOS, days	10.9d	11.5d	MD: -0.62 (95% CI: -1.48-0.25)	0.162
In-hospital mortality, %	3.3	5.5	OR: 0.58 (95% CI: 0.40–0.82)	0.003
Risk of re-hospitalization, %	29	37	OR: 0.72 (95% CI: 0.62–0.82)	< 0.001
ICU admission, %	16	14	OR: 1.23 (95% CI: 1.04–1.46)	0.016
Aspergillosis, %	0.2	0.2	OR: 1.15 (95% CI: 0.14–4.27)	0.694

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		
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 sub-groups. 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

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 improvments 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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References

1. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, Aichour AN, Aichour I, Aichour MTE, Alam K, Alam N, Alkaabi JM, Al-Maskari F, Alvis-Guzman N, Amberbir A, Amoako YA, Ansha MG, Antó JM, Asayesh H, Atey TM, Avokpaho EFGA, Barac A, Basu S, Bedi N, Bensenor IM, Berhane A, Beyene AS, Bhutta ZA, Biryukov S, Boneya DJ, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir. Med.* [Internet] Elsevier; 2017; 5: 691–706Available from: https://www.sciencedirect.com/science/article/pii/S221326001730293X?via%3Dihub.
2. Hoyert DL, Xu J. Deaths: preliminary data for 2011. *Natl. Vital Stat. Rep.* [Internet] 2012; 61: 1–51Available from: http://www.ncbi.nlm.nih.gov/pubmed/24984457.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, AlMazroa MA, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* [Internet] Elsevier; 2012; 380: 2095–2128Available from: https://www.sciencedirect.com/science/article/pii/S0140673612617280?via%3Dihub.
4. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon. Outcomes Res.* [Internet] Dove Press; 2013; 5: 235–245Available from: http://www.ncbi.nlm.nih.gov/pubmed/23818799.
5. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* [Internet] Elsevier; 2007; 370: 741–750Available from: https://www.sciencedirect.com/science/article/pii/S0140673607613774?via%3Dihub.

6. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and Airway Inflammation in Chronic Obstructive Pulmonary Disease Severe Exacerbations. *Am. J. Respir. Crit. Care Med.* [Internet] American Thoracic Society; 2006; 173: 1114–1121Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.200506-859OC.
7. Sethi S, Murphy TF. Infection in the Pathogenesis and Course of Chronic Obstructive Pulmonary Disease. *N. Engl. J. Med.* [Internet] Massachusetts Medical Society; 2008; 359: 2355–2365Available from: http://www.nejm.org/doi/abs/10.1056/NEJMra0800353.
8. Rohde G, Wiethege A, Borg I, Kauth M, Bauer TT, Gillissen A, Bufe A, Schultze-Werninghaus G. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: A case-control study. *Thorax* 2003; 58: 37–42.
9. Centers for Disease Control and Prevention. Guide for considering influenza testing when influenza viruses are circulating in the community [Internet]. 2019 [cited 2020 Feb 13].Available from: https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm.
10. Influenza (Saisonale Grippe) » Guidelines.ch [Internet]. [cited 2020 May 19].Available from: https://kssg.guidelines.ch/guideline/1727/6355.
11. COPD Global Initiative. 2020 Report [Internet]. Glob. Initiat. Chronic Obstr. Lung Dis. 2020Available from: https://goldcopd.org/gold-reports/.
12. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* [Internet] John Wiley & Sons, Ltd; 2014; Available from: http://doi.wiley.com/10.1002/14651858.CD001288.pub4.
13. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst. Rev.* [Internet] John Wiley & Sons, Ltd; 2016; Available from: http://doi.wiley.com/10.1002/14651858.CD010406.pub2.
14. Siemieniuk RAC, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander PE, Fei Y, Vandvik PO, Loeb M, Guyatt GH. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and metaanalysis. *Ann. Intern. Med.* 2015; 163: 519–528.
15. Briel M, Spoorenberg SMC, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, Gabarrús A, Blum CA, Confalonieri M, Kasenda B, Siemieniuk RAC, Boersma W, Bos WJW, Christ-Crain M, Ovidius Study Group CSG and SSG. Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis. *Clin. Infect. Dis.* [Internet] 2017; 66: 346–354Available from: https://doi.org/10.1093/cid/cix801.
16. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and treatment of adults with community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.* 2019; 200: E45–E67.
17. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, Winzeler B, Bingisser R, Elsaesser H, Drozdov D, Arici B, Urwyler SA, Refardt J, Tarr P, Wirz S, Thomann R, Baumgartner C, Duplain H, Burki

D, Zimmerli W, Rodondi N, Mueller B, Christ-Crain M. Adjunct prednisone therapy for patients with community-acquired pneumonia: A multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015;.

18. Ewig S et al. S3-Leitlinie - Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie und Prävention - Update 2016 [Internet]. 2016Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-020l_S3_ambulant_erworbene_Pneumonie_Behandlung_Praevention_2016-02-2.pdf.
19. Myles P, Nguyen-van-tam JS, Semple MG, Brett SJ, Bannister B, Read RC, Taylor BL, Mcmenamin J, Enstone JE, Nicholson KG, Openshaw PJ, Lim WS. Differences between asthmatics and nonasthmatics hospitalised with influenza A infection. *Eur Respir J* 2016; 41: 824–831.
20. Bundesamt für Statistik. Medizinische Statistik der Krankenhäuser [Internet]. Available from: .
21. Albrich WC, Rassouli F, Waldeck F, Berger C, Baty F. Influence of Older Age and Other Risk Factors on Pneumonia Hospitalization in Switzerland in the Pneumococcal Vaccine Era. *Front. Med.* 2019; 6: 1–10.
22. Bundesamt für Gesundheit. Saisonale Grippe – Lagebericht Schweiz [Internet]. [cited 2020 May 19].Available from: https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/saisonale-grippe---lagebericht-schweiz.html.
23. Chartrand C, Leeflang MMG, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: A meta-analysis. *Ann. Intern. Med.* 2012; 156: 500–511.
24. Merckx J, Wali R, Schiller I, Caya C, Gore GC, Chartrand C, Dendukuri N, Papenburg J. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction: A Systematic Review and Meta-analysis. *Ann. Intern. Med.* [Internet] 2017; 167: 394–409Available from: https://doi.org/10.7326/M17-0848.
25. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* United States; 2000; 161: 1608–1613.
26. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* United States; 2004; 1: 115–120.
27. World Health Organization. Clinical management of human infection with avian influenza A (H5N1) virus [Internet]. Clin. Manag. Hum. Infect. with avian Influ. A virus 2007Available from: https://www.who.int/influenza/resources/documents/ClinicalManagement07.pdf.
28. Dusemunda F, Chronisb J, Batya F, Albrichc WC, Martin H. The outcome of community-acquired pneumonia in patients with chronic lung disease: A case-control study. *Swiss Med. Wkly.* 2014; 144: 1–8.
29. Kwak HJ, Park DW, Kim JE, Park MK, Koo GW, Park TS, Moon J-Y, Kim TH, Sohn JW, Yoon HJ, Shin DH, Kim S-H. Prevalence and Risk Factors of Respiratory Viral Infections in Exacerbations of Chronic Obstructive Pulmonary Disease. *Tohoku J. Exp. Med.* Japan; 2016; 240: 131–139.

30. Ko FWS, Ip M, Chan PKS, Chan MCH, To K-W, Ng SSS, Chau SSL, Tang JW, Hui DSC. Viral etiology of acute exacerbations of COPD in Hong Kong. *Chest* 2007; 132: 900–908.
31. McManus TE, Marley A-M, Baxter N, Christie SN, O'Neill HJ, Elborn JS, Coyle P V, Kidney JC. Respiratory viral infection in exacerbations of COPD. *Respir. Med.* 2008; 102: 1575–1580.
32. Mulpuru S, Li L, Ye L, Hatchette T, Andrew MK, Ambrose A, Boivin G, Bowie W, Chit A, Dos Santos G, ElSherif M, Green K, Haguinet F, Halperin SA, Ibarguchi B, Johnstone J, Katz K, Langley JM, LeBlanc J, Loeb M, MacKinnon-Cameron D, McCarthy A, McElhaney JE, McGeer A, Powis J, Richardson D, Semret M, Shinde V, Smyth D, Trottier S, et al. Effectiveness of Influenza Vaccination on Hospitalizations and Risk Factors for Severe Outcomes in Hospitalized Patients With COPD. *Chest* United States; 2019; 155: 69–78.
33. Viniol C, Vogelmeier CF. Exacerbations of COPD. *Eur. Respir. Rev. an Off. J. Eur. Respir. Soc.* England; 2018; 27.
34. Lee N, Chan PKS, Hui DSC, Rainer TH, Wong E, Choi K-W, Lui GCY, Wong BCK, Wong RYK, Lam W-Y, Chu IMT, Lai RWM, Cockram CS, Sung JJY. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J. Infect. Dis.* [Internet] The University of Chicago Press; 2009; 200: 492–500Available from: https://pubmed.ncbi.nlm.nih.gov/19591575.
35. Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, Wu J, Lan L, Yang S. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci. Rep.* [Internet] Nature Publishing Group UK; 2020; 10: 3044Available from: https://pubmed.ncbi.nlm.nih.gov/32080223.
36. Yin T, Zhu Z, Mei Z, Feng J, Zhang W, He Y, Shi J, Qian L, Liu Y, Huang Q, Hu Y, Jie Z. Analysis of viral infection and biomarkers in patients with acute exacerbation of chronic obstructive pulmonary disease. *Clin. Respir. J.* 2018; 12: 1228–1239.

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