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Review Article

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A Review of the Impact of Secondary Infections from COVID-19

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The prevalence, treatment, and impact of secondary bacterial and fungal infections in patients with COVID-19 have been of significant interest as the mortality for such patients is substantially higher than for patients without a secondary infection. The objective of this article is to provide an up-to-date quantitative perspective on the rate of secondary infections based on all available data published before August 15th 2020.

In the 1918 Spanish flu pandemic more than half of the 50 million worldwide deaths are believed to have been caused principally by secondary infections (D. Morens 2008). To minimize the impact of COVID-19 it is critical to understand the factors, which may determine risk for secondary infections. These may be co-morbidities, hospitalization (with exposure to nosocomial pathogens), care patterns, etc. Further, we need to understand the effectiveness and appropriateness of the current widespread administration of broad-spectrum antibiotics for different patient groups.

The secondary infections from COVID-19 are also calling increased attention to the simultaneous pandemic of antimicrobial resistance (AMR). The two pandemics are moving at different speeds but AMR will persist for many more years and will likely kill many more people in total (at least 700,000 die from AMR every year whereas COVID-19 has killed 1,300,000 so far as of mid-November 2020). How much one is affecting the other and vice versa is not yet known.

The first journal paper to specifically quantify the secondary infection problem for COVID-19 with more than 100 patients was F. Zhou et al. published on March 9, 2020. The summary finding from 191 confirmed COVID-19 patients treated in Wuhan, China was that about 15% of patients had secondary infections and that those patients contributed to about half of the deaths. These early data were widely cited also in the popular press.

T. Rawson et al. published a review of several further articles covering in total 806 patients on May 2, 2020 (a total of 9 papers, including the paper from F. Zhou) finding that a mere 8% of those patients had a secondary infection. Due to the explosion of data collection and publications during the COVID pandemic, several papers were submitted before Rawson's review was published, which were not included, and several have been published since that time. One such paper (X. Zhu et al.) reported an astonishing 94% co-infections and another (Bhatraju) found zero, suggesting substantial heterogeneity. In the summary table below, I report on all the published data that we have been able to find in PubMed as of August 15th.

Based on the data to date, the main conclusions are:
Secondary bacterial and fungal infections occur in COVID-19 patients just as previously seen with influenza, and other viral respiratory diseases increasing the risk of death.

- The best estimate of the rate of secondary infections appears to be 5-6%. However, the rate is very heterogenous and thus still difficult to assess. Further exacerbating this issue is that different studies report on different patient populations (some reporting on children only, some on the elderly only, and not all are looking for the same bacterial and fungal pathogens).
- The rate of secondary infections is likely lower in the developed world (Selpuveda and Rawson) than in the developing world (closer to that reported by F. Zhou namely around 15-20%). This is based on the total sum of data to date excluding what appears to be outlier data from X.Zhu et al.
- There is no evidence so far that widespread empiric use of antibiotics is saving lives. This practice may exacerbate the spread of AMR, although there is also not yet solid evidence that is specific to the current pandemic.

Despite the millions of COVID-19 patients that have been diagnosed around the world, the preponderance of data covering secondary infections is still only a few thousand patients. Further, given that the majority of these reported patients are from China, making any conclusion from outside that geography tenuous. The most prevalent pathogens are also only reported in about half of the publications leaving a significant question as to whether there is commonality across geographies (i.e., that COVID-19 patients are particularly susceptible to certain pathogens) or whether the secondary infections are the same as the prior local distribution. The reported data also does not yet support any conclusions on correlation with co-morbidities as co-morbidities are also only reported in few of the publications. Given the scarcity of data, it is too early to make a call on whether the high rates of empiric antibiotic administration (widely reported to be greater than 70%) should be tempered.

I urge clinicians to report on secondary infections in COVID-19 patients in greater granularity on all infection types, comorbidities, demographics, pathogens tested for and found including susceptible/resistant strains, as well as antibiotic treatment regimens. The data is available but is often incompletely reported. For example, J. Sepulveda et al. published on 28,011 patients in New York but only on bacteremia from blood cultures with no data on pneumonia or antibiotic susceptibility results. We need these larger more granular data sets published in order to understand the risk factors of secondary infections including AMR and create appropriate medical treatment guidelines.

Date	Author	Region	Number of co-infection	Comments
Feb-20	L. Ling, et al.	Hong Kong	2/49 (4.1%)	After 48 hours of admission to the ICU
Feb-20	X. Zhu, et al.	Jiangsu Province	242/257 (94%)	Not hospitalized except 3 patients admitted to ICU; no deaths reported
Feb-20	L. Wang, et al.	Wuhan, China	145/339 (43%)	All patients over the age of 60
Feb-20	F. Wu, et al.	Wuhan, China	76/1048 (7%)	Patients with COPD had higher coinfection rates
Feb-20	X. Yang, et al.	Wuhan, China	5/52 (10%)	All patients critically ill
Mar-20	J. Sepulveda, et al.	New York City	1064/28,011 (3.8%)	COVID-negative patients had more co-infetions
Mar-20	X. Li, et al.	Wuhan, China	22/25 (88%)	Only patients who died
Mar-20	Z. Yang, et al.	Wuhan, China	N/A	Patients receiving corticoid steroids at higher risk of bacterial infections
Mar-20	L.Xiao, et al.	Honghu and Nanchang, China	296/442 (67%)	Secondary infection is a significant morbidity risk factor
Mar-20	X. Dong, et al.	Wuhan, China	1/11 (9%)	Detailed lab results presented
Apr-20	H, Li, et al.	Wuhan, China	13/40 (32%)	Hospitalized children only
Apr-20	B. Langford, et al.	Canada	230/3339 (6.9%)	Meta-ananlysis
Apr-20	A. Alanio, et al.	France	9/27 (33%)	Looking For aspergillosis only
Apr-20	Koehler, et al.	Germany	5/19 (26%)	Looking For aspergillosis only
May-20	M. Pulia, et al	Wisconsin, USA	N/A	Testing for both viral and bacterial infection
May-20	J. Toubiana, et al	Paris, France	16/21 (76%)	Children and adolescents with Kawasaki disease
May-20	T. Rawson, et al.	Review	62/806 (8/%)	Review article of 9 prior publications. Note mistake in chen et al.actually reported 5 not 2 co-infections
May-20	P. Bharaju, et al.	Hongzhou, China	Data covered elsewhere in table	Phage therapy may be used to used to treat secondary infections
May-20	P. Manohar, et al.	WA, USA	0/24 (0%)	All hospitalized
Jun-20	TJ Cooper,et al.	New York	4/21 (19%)	HIV+ patients
Jul-20	L. Zhang et al.	Wuhan, China	5/28 (28%)	Pregnant patients
Jul-20	Y. Wu, et al.	Wuhan, China	Unspecified/71	Severely sick patients had more secondary infections
Jul-20	J. Qu, et al	4 Provinces, China	66/246 (27%)	Comparison to influenza
		Total	2263/34805	26 papers including 9 from Rawson
		Total (w/o Zhu)	2021/34548 (5.8%)	Zhu appears to be an outlier so could be excluded

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