The Daily COVID-19 Literature Surveillance Summary

August 19, 2020

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COVID-19 Daily Literature Surveillance

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
*OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

EXECUTIVE SUMMARY

Climate
- A survey of 335 nephrology clinic staff in India sought to assess perceived negative stigma from being a healthcare worker during the COVID-19 pandemic. The results showed that 54.6% of staff perceived significant stigma due their job, 36.1% of staff reported significant stress, and a strong correlation was shown between perceived stigma and stress.

Epidemiology
- A cross-sectional study in Spain investigated the presence of SARS-CoV-2 RNA fecal shedding at six wastewater treatment plants by testing 42 inflowing samples, 18 secondary treated outflowing samples, and 12 tertiary treated outflowing samples. They found SARS-CoV-2, positive by RT-PCR, in 87% of inflowing, 11% of secondary treated, and 0% of tertiary treated samples suggesting that wastewater analysis may provide alternative and effective environmental surveillance for SARS-CoV-2 fecal shedding and could help to direct public health response in certain communities.
- A mathematical model devised by group from Stockholm University reveals a herd immunity level to COVID-19 of about 43% when taking into account population heterogeneity by adjusting for age and social activity in a structured community.

Understanding the Pathology
- Investigators in Wuhan found that SARS-CoV-2, compared to six other coronavirus protein sequences, has distinct viral coding protein sequences that promote host responsive gene expression patterns such as increasing neutrophil activity and expression of key transcriptional factors. This matches data that show that show increases in blood neutrophil levels in severe COVID-19 patients and provides a mechanistic framework for the pathogenesis of SARS-CoV-2 infection.

Transmission & Prevention
- An infectious disease physician at NYU Langone Vaccine Center discussed an inactivated protein immunogen proposed by Xia et al, 2020 as a COVID-19 vaccine candidate that was well-tolerated in phase 1 (n=96 adults) and phase 2 (n=224 adults) and induced SARS-CoV-2 neutralizing antibodies 14 days after the last booster vaccination, with most common side effects being self-limiting fever and injection site pain. The author suggests β-propiolactone–inactivated SARS-CoV-2 plus adjuvant as a potential vaccine candidate given its tolerability, safety, and ability to generate an immune response.

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COVID-19-RELATED STIGMA AND PERCEIVED STRESS AMONG DIALYSIS STAFF

BLUF

An interdisciplinary group of researchers from the Departments of Psychiatry and Nephrology at the Iqraa International Hospital and Research Centre in India performed a survey of 335 nephrology clinic staff between April 26 and July 7, 2020 to assess perceived negative stigma from being a healthcare worker during the COVID-19 pandemic. The survey was assessed with a Perceived Stress Scale-10 (PSS-10) and the results showed that:
• 54.6% of staff perceived significant stigma due their job
• 36.1% of staff reported significant stress
• A strong correlation was shown between stigma and PSS-10 scores (0.266, p<.01)
This study suggests that healthcare workers can face stigma from public, family and friends due to their COVID-19 exposures as healthcare workers and steps should be taken to mitigate this stigma for the well-being of healthcare workers.

SUMMARY

Healthcare workers are at risk from not only COVID-19 exposure but from mental stress and anguish from their jobs and stigma from the public as perceived vectors of COVID-19. The authors state that "stigma from friends and family as they work in hospital environments, a high-risk area for SARS-CoV-2 contamination" and that "stigma compounds the stress levels of healthcare staff thereby affecting job satisfaction and quality of patient care. Stigma is associated with violence against healthcare workers: more than 200 attacks on healthcare workers and health facilities during the ongoing pandemic were reported by May 2020."

This survey was used to assess perceived stigma these healthcare workers face. The group surveyed consisted of 335 people, the majority dialysis technicians or nurses. The authors state that in regard to survey design, "Stress among the dialysis staff was assessed by the Perceived Stress Scale-10 (PSS-10) which contains 10 items, each of which is scored on a 5-point Likert scale. The total score ranges between 0 and 40, with a higher score indicating higher perceived stress."

SARS-COV-2 RNA IN WASTEWATER ANTICIPATED COVID-19 OCCURRENCE IN A LOW PREVALENCE AREA

Randazzo W, Truchado P, Cuevas-Ferrando E, Simón P, Allende A, Sánchez G.. Water Res. 2020 Aug 15;181:115942. doi: 10.1016/j.watres.2020.115942. Epub 2020 May 16.

BLUF

A cross-sectional study by authors affiliated with food safety in Spain investigated the presence of SARS-CoV-2 RNA fecal shedding at six wastewater treatment plants (WWTPs; Figure 1) by testing 42 inflowing samples, 18 secondary treated outflowing samples, and 12 tertiary treated outflowing samples from March 12th, 2020 to April 14th, 2020 and found SARS-CoV-2 positive RT-PCR in 87% of inflowing, 11% of secondary treated, and 0% of tertiary treated samples (Figure 2). Authors suggest wastewater analysis may provide alternative and effective environmental surveillance for SARS-CoV-2 fecal shedding to direct public health response in certain communities, especially those with limited capacity for clinical testing.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 200,000 reported COVID-19 cases in Spain resulting in more than 20,800 deaths as of April 21, 2020. Faecal shedding of SARS-CoV-2 RNA from COVID-19 patients has extensively been reported. Therefore, we investigated the occurrence of SARS-CoV-2 RNA in six wastewater treatments plants (WWTPs) serving the major municipalities within the Region of Murcia (Spain), the area with the lowest COVID-19 prevalence within Iberian Peninsula. Firstly, an aluminum hydroxide adsorption-precipitation concentration method was validated using a porcine coronavirus (Porcine Epidemic Diarrhea Virus, PEDV) and mengovirus (MgV). The procedure resulted in average recoveries of 10 +- 3.5% and 10 +- 2.1% in influent water (n = 2) and 3.3 +- 1.6% and 6.2 +- 1.0% in effluent water (n = 2) samples for PEDV and MgV, respectively. Then, the method was used to monitor the occurrence of SARS-CoV-2 from March 12 to April 14, 2020 in influent, secondary and tertiary effluent water samples. By using the real-time RT-PCR (RT-qPCR) Diagnostic Panel validated by US CDC that targets three regions of the virus nucleocapsid (N) gene, we estimated quantification of SARS-CoV-2 RNA titers in untreated wastewater waters of 5.4 +- 0.2 log10 genomic copies/L on average. Two secondary water samples resulted positive (2 out of 18) and all tertiary water samples tested as negative (0 out 12). This environmental surveillance data were compared to declared COVID-19 cases at municipality level, revealing that members of the community were shedding SARS-CoV-2 RNA in their stool even before the first cases were reported by local or national authorities in many of the cities where wastewaters have been sampled. The detection of SARS-CoV-2 in wastewater in early stages of the spread of COVID-19 highlights the relevance of this strategy as an early indicator of the infection within a specific population. At this point, this environmental surveillance could be implemented by municipalities right away as a tool, designed to help authorities to coordinate the exit strategy to gradually lift its coronavirus lockdown.
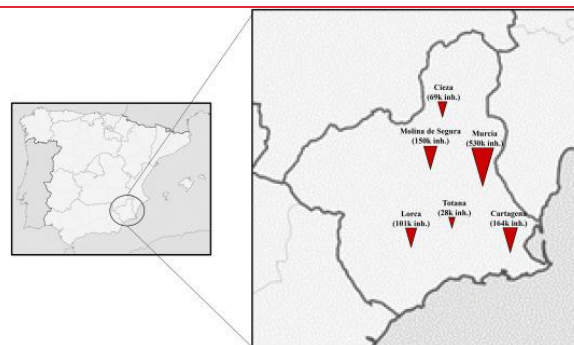
FIGURES

Figure 1. Maps of the sampling location. Symbols represents waste water treatment plants (WWTPs) and are sized according to the number of equivalent inhabitants (inh.).

Figure 2. Mean amplification cycles of SARS-CoV-2 RNA in influent, secondary and tertiary effluent waters in monitored WWTPs within Murcia Region (Spain). Results are reported for each of the three regions of the virus nucleocapsid (N) gene according to the first version of the Real-Time RT-PCR Diagnostic Panel by US CDC. Abbreviations: -, negative; whiteboxes, not tested.

MODELING

A MATHEMATICAL MODEL REVEALS THE INFLUENCE OF POPULATION HETEROGENEITY ON HERD IMMUNITY TO SARS-COV-2

BLUF

Authors from Stockholm University devised a mathematical model that reveals a herd immunity level to COVID-19 of about 43% (Ro=2.5) when adjusting for age and social activity in a structured community (Table 1). Their model also reveals that ending severe preventive measures in a community is associated with a strong second wave of cases, while ending less severe preventive measures is not associated with a strong second wave of cases (albeit with greater initial peak incidences; Figure 1, 2). These findings suggest that population heterogeneity does influence herd immunity levels, especially when comparing to the herd immunity level (60%) based on a homogenous population model. Further, the authors suggest that lifting preventive measures gradually and utilizing milder restrictions may prevent a strong second wave of infections.

SUMMARY

The model stratified populations into 6 age groups and 3 arbitrary social interaction groups (high, average, low). Each stratification was designated its own coefficient in the model. The model also assumed that infected individuals remained latent for 3 days and infectious for 4 days. The severity of preventive measures was denoted by the character alpha; the model assumes the alpha coefficient is less than 1 during preventive measures and alpha = 1 after the preventive measures have ceased. The model implements first incidence at day 0, preventive measures implemented at day 30, and preventive measures retracted at day 135. The findings show that severe preventive measures does decrease initial peak incidence of COVID-19, but also results in a second wave of cases even greater than the first after preventive measures have been retracted. However, cumulative cases of severe preventive measures are greater than moderate preventive measures but fewer than light preventive measures. While no preventive measures does indeed achieve herd immunity, the initial peak of cases is much greater than the light, moderate, and severe preventive measures. Furthermore, cumulative cases of zero preventive measures were found to be greater than cumulative cases in all other groups. The researchers noted that their model's parameters does not adequately consider the sheer heterogeneity of human interaction and susceptibility, and recommend using the model as a guideline rather than an epidemiological plan.

ABSTRACT

Despite various levels of preventive measures, in 2020 many countries have suffered severely from the coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. We show that population heterogeneity can significantly impact disease-induced immunity as the proportion infected in groups with the highest contact rates is greater than in groups with low contact rates. We estimate that if R 0 = 2.5 in an age-structured community with mixing rates fitted to social activity then the disease-induced herd immunity level can be around 43%, which is substantially less than the classical herd immunity level of 60% obtained through homogeneous immunization of the

population. Our estimates should be interpreted as an illustration of how population heterogeneity affects herd immunity, rather than an exact value or even a best estimate.
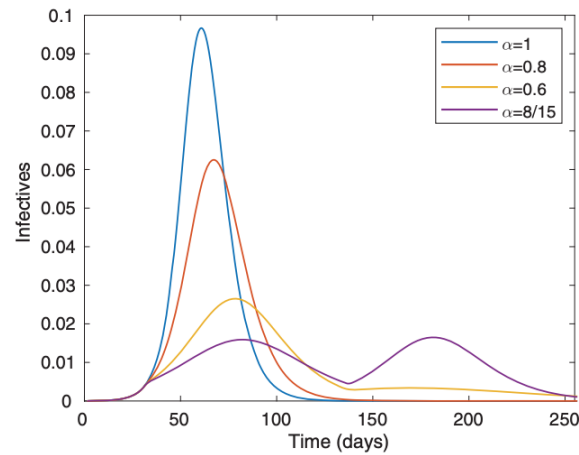
FIGURES

Fig. 1. Overall fraction infected over time. Shown is a plot of the overall fraction
infected over time for the age and activity structured community with R0 = 2.5 for four different preventive levels inserted 15 March (day 30) and lifted 30 June (day 135). The blue, red, yellow, and purple curves correspond to no, light, moderate, and severe preventive measures, respectively.
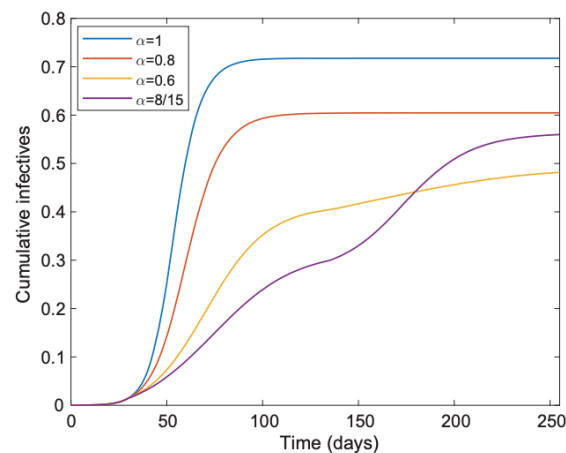

Fig. 2. Cumulative fraction infected over time. Shown is a plot of the cumulative fraction infected over time for the age and activity structured community and R0 = 2.5 for four different preventive levels inserted 15 March (day 30) and lifted 30 June (day 135). The blue, red, yellow, and purple curves correspond to no, light, moderate, and severe preventive measures, respectively.

Table 1. Disease-induced herd immunity level h_D and classical herd immunity level h_C for different population structures. Numbers correspond to percentages.

Population structure	$R_0 = 2.0$		$R_0 = 2.5$		$R_0 = 3.0$	
	h_D	h_C	h_D	h_C	h_D	h_C
Homogeneous	50.0	50.0	60.0	60.0	66.7	66.7
Age structure	46.0	50.0	55.8	60.0	62.5	66.7
Activity structure	37.7	50.0	46.3	60.0	52.5	66.7
Age and activity structure	34.6	50.0	43.0	60.0	49.1	66.7

MECHANISTIC INSIGHTS INTO SARS-COV-2 EPIDEMIC VIA REVEALING THE FEATURES OF SARS-COV-2 CODING PROTEINS AND HOST RESPONSES UPON ITS INFECTION

BLUF

Authors affiliated with Wuhan Huoshenshan Hospital, China found that the SARS-CoV-2 infection, compared to six other coronavirus protein sequences (Table 1), has distinct viral coding protein sequences that promote host responsive gene expression patterns such as increasing neutrophil activity and expression of key transcriptional factors (Figure 6). Observations of blood neutrophil samples from patients (n=2976) diagnosed with SARS-CoV-2 showed an abnormal increase in neutrophils, correlating with severe illness and death (Figure 5). This study suggests a mechanistic framework for the pathogenesis of SARS-CoV-2 infection to assist the development of therapies against SARS-CoV-2.

ABSTRACT

: There are seven known coronaviruses that infect humans: four mild coronaviruses, including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, only cause mild respiratory diseases, and three severe coronaviruses, including SARS-CoV, MERS-CoV and SARS-CoV-2, can cause severe respiratory diseases even death of infected patients. Both infection and death caused by SARS-CoV-2 are still rapidly increasing worldwide. In this study, we demonstrate that viral coding proteins of SARS-CoV-2 have distinct features and are most, medium and least conserved with SARS-CoV, MERS-CoV, and the rest four mild coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1), respectively. Moreover, expression of host responsive genes (HRG), HRG-enriched biological processes, and HRG-enriched KEGG pathways upon infection of SARS-CoV-2 show slightly overlapping with SARS-CoV and MERS-CoV but distinctive to the four mild coronaviruses. Interestingly, enrichment of overactivation of neutrophil by HRGs is only and commonly found in infections of severe SARS-CoV-2, SARS-CoV, and MERS-CoV but not in the other four mild coronaviruses, and the related gene networks show different patterns. Clinical data supports that overactivation of neutrophil for severe patients can be one major factor for the similar clinical symptoms observed in SARS-CoV-2 infection compared to infections of the other two severe coronavirus (SARS-CoV, and MERS-CoV). Taken together, our study provides a mechanistic insight into SARS-CoV-2 epidemic via revealing the conserved and distinct features of SARS-CoV-2, raising the critical role of dysregulation of neutrophil for SARS-CoV-2 infection. SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.
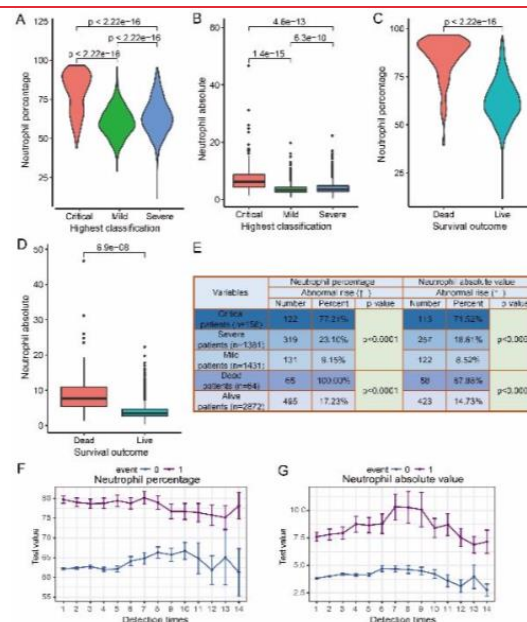
FIGURES

Figure 5: Verify the correlation between neutrophils and clinical severe diseases caused by SARS-CoV-2. A: The violin diagram shows neutrophil percentage in different classification. B: The box chart shows neutrophil absolute value in different classification. C: The violin diagram shows neutrophil percentage in different survival outcome. D: The box chart shows neutrophil absolute value in different survival outcome. E: Statistics on the number and proportion of neutrophil abnormalities in different classification and survival outcome. The first test value of admission is used. The reference ranges of normal neutrophil percentage and absolute value are 40 ~ 75 (40% ~ 75%) and 1.8 ~ 6.3 (*109 / L), respectively. F: The dynamic change curve of neutrophil percentage during hospitalization. G: The dynamic curve of neutrophil absolute value during hospitalization. Each point represents the average of different detection times increasing with length of hospitalization, and the standard error was displayed. The two-tailed t-test was used to calculate the significance of continuous variables, and the chi-square test was used to analyze the significance of frequency. Event 1 represents the patients who developed critical illness or died or admitted to the ICU while event 0 represents patients with better symptoms and prognosis.

Table 1. Similarity of the protein sequences obtained by comparing SARS-CoV-2 with other six infected human coronavirus proteins sequence and genomic sequence.

| SARS-CoV-2	SARS-CoV	MERS-CoV	HCoV-229E	HCoV-NL63	HCoV-OC43	HCoV-HKU1
ORF6	93.44%	22.95%	27.87%	18.03%	29.51%	18.03%
Membrane protein	98.20%	62.61%	66.05%	63.16%	70.84%	63.16%
Envelope protein	97.37%	58.67%	48.05%	29.33%	54.86%	29.33%
ORF3a	90.55%	11.21%	6.18%	8.00%	5.45%	8.00%
ORF10	92.11%	44.74%	28.95%	42.11%	42.10%	42.11%
ORF8	20.94%	15.70%	11.57%	13.22%	19.01%	13.22%
Surface glycoprotein	87.35%	39.51%	28.66%	24.04%	39.26%	24.04%
ORF7a	95.90%	14.05%	9.92%	14.05%	15.70%	14.05%
Nucleocapsid phosphoprotein	97.16%	68.49%	37.14%	27.98%	53.26%	27.98%
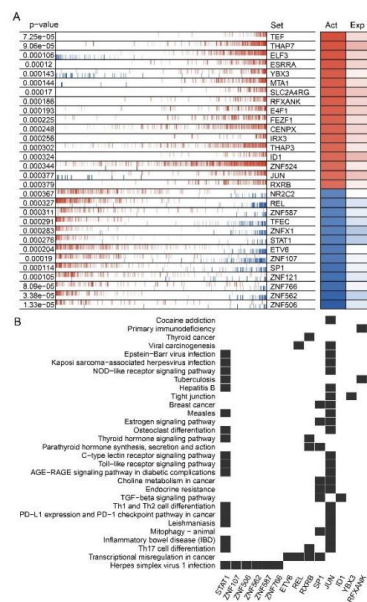
Fig 6. A: VIPER plot showing the projection of the negative (repressed, shown in blue color) and positive (activated, shown in red color) targets for top 30 MRs, as inferred by ARACNe and correlation analysis when reverse engineering the regulatory network (vertical lines resembling a bar-code), on the GES (x-axis), where the genes in the GES were rank-sorted from the one most down-regulated to the one most upregulated in the 'SARS-CoV-2 positive' vs 'SARS-CoV-2 negative' conditions. The two-columns heatmap displayed on the right side of the Fig shows the inferred differential activity (first column) and differential expression (second column), with the rank of the displayed genes in the GES (shown all the way to the right). B: The KEGG signaling pathway analysis of the top 30 MRs. The first 30 significantly enriched KEGG items are displayed and the detailed contents refer to Table S8.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

AN INACTIVATED VIRUS CANDIDATE VACCINE TO PREVENT COVID-19

BLUF

An infectious disease physician at NYU Langone Vaccine Center of NYU Grossman School of Medicine, New York discussed an inactivated protein immunogen (β-propiolactone–inactivated SARS-CoV-2 virus adjuvanted in 0.5 mg aluminum hydroxide) proposed by Xia et al, 2020 as a COVID-19 vaccine candidate that was well-tolerated in phase 1 (n=96 adults) and phase 2 (n=224 adults) and induced SARS-CoV-2 neutralizing antibodies 14 days after the last booster vaccination, with most common side effects being self-limiting fever and injection site pain. The author suggests β-propiolactone–inactivated SARS-CoV-2 plus adjuvant as a potential vaccine candidate given its tolerability, safety, and ability to generate an immune response.

EMERGENCY MEDICINE

THE IMPACT OF PATIENT ISOLATION ON EMERGENCY DEPARTMENT LENGTH OF STAY: A RETROSPECTIVE COHORT STUDY USING THE REGISTRY FOR EMERGENCY CARE (REC-1)

O'Reilly GM, Mitchell RD, Mitra B, Noonan MP, Hiller R, Brichko L, Luckhoff C, Paton A, Smit DV, Cameron PA.. Emerg Med Australas. 2020 Aug 14. doi: 10.1111/1742-6723.13607. Online ahead of print.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)

BLUF

A retrospective study of patients (n=447) who presented to the emergency department (ED) of The Alfred Hospital Emergency & Trauma Centre between May 18 to May 31, 2020 found that the median ED length of stay (LOS) for isolation patients (n=123) was 210 to 377 minutes versus 126 to 297 minutes for those that did not require isolation (difference in ED LOS medians = 55 minutes; p less than 0.001; Figure 1). This finding suggests that isolated patients may be delayed in leaving the ED or arriving at their final in-patient destination for treatment, highlighting one of the downfalls of isolation management protocols.

ABSTRACT

OBJECTIVE: The number of patients with suspected COVID-19 presenting to Australian Emergency Departments (EDs) continues to impose a burden on healthcare services. Isolation is an important aspect of infection prevention and control (IPC), but has been associated with undesirable consequences among hospital inpatients. The aim of this study was to determine if isolation is associated with an increased length of stay (LOS) in the ED. METHODS: The REC Project is a prospective cohort study with a series of nested sub-studies. The present study was a retrospective analysis of adult patients allocated an Australasian Triage Scale category of 1 or 2 who presented to a tertiary ED between 18-31st May 2020. The primary outcome was ED LOS. Regression methods were used to determine the independent association between ED isolation and LOS. RESULTS: There were 447 patients who met inclusion criteria, of which 123 (28%) were managed in isolation. The median (IQR) ED LOS was 259 (210-377) minutes for the isolation group and 204 (126-297) minutes for the non-isolation group, a difference in median ED LOS of 55 min (p < 0.001). Isolation was independently associated with a 23% increase in ED LOS (p = 0.002) and doubled the odds of an ED stay of more than 4 h (adjusted OR 2.2 [1.4-3.4], p = 0.001). CONCLUSIONS: Consistent with the anecdotal experience of Australian ED clinicians, this study demonstrated an increased ED LOS for patients managed in isolation. Enhanced IPC precautions will be required during and beyond the current pandemic, creating significant ongoing challenges for emergency care systems.
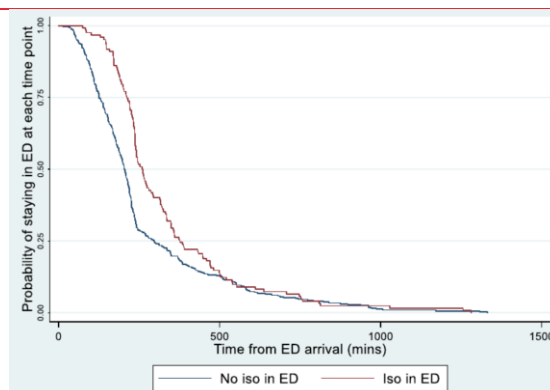
FIGURES

Figure 1: Kaplan-Meier plot for probability of continuing to stay in ED. Log-rank test for equality of survivor functions: p=0.001

CROSSTALK BETWEEN ENDOPLASMIC RETICULUM STRESS AND ANTI-VIRAL ACTIVITIES: A NOVEL THERAPEUTIC TARGET FOR COVID-19

BLUF

A literature review by cell biologists and immunologists affiliated with University of Maryland School of Medicine in Baltimore found andrographolide (isolated from the Andrographis paniculata plant) and melatonin both mitigated endoplasmic reticulum (ER) stress and unfolding protein response (UPR) triggered by accumulation of misfolded proteins (as seen during SARS-CoV-2 infection) via anti-inflammatory, antioxidant, and other immune enhancing actions (Figure 1). Authors suggest andrographolide and melatonin combination therapy could be a cost-efficient, low risk, and effective alternative or adjuvant to drugs currently being explored for COVID-19 treatment.

ABSTRACT

The outbreak of COVID-19 caused by 2019-nCov/SARS-CoV-2 has become a pandemic with an urgent need for understanding the mechanisms and identifying a treatment. Viral infections including SARS-CoV are associated with increased levels of reactive oxygen species, disturbances of Ca++ caused by unfolded protein response (UPR) mediated by endoplasmic reticulum (ER) stress and is due to the exploitation of virus's own protein i.e., viroporins into the host cells. Several clinical trials are ongoing including testing Remdesivir (anti-viral), Chloroquine and Hydroxychloroquine derivatives (anti-malarial drugs) etc. Unfortunately, each drug has specific limitations. Herein, we review the viral protein involvement to activate ER stress transducers (IRE-1, PERK, ATF-6) and their downstream signals; and evaluate combination therapies for COVID-19 mediated ER stress alterations. Melatonin is an immunoregulator, anti-pyretic, antioxidant, anti-inflammatory and ER stress modulator during viral infections. It enhances protective mechanisms for respiratory tract disorders. Andrographolide, isolated from Andrographis paniculata, has versatile biological activities including immunomodulation and determining SARS-CoV-2 binding site. Considering the properties of both compounds in terms of anti-inflammatory, antioxidant, anti-pyrogenic, anti-viral and ER stress modulation and computational approaches revealing andrographolide docks with the SARS-CoV2 binding site, we predict that this combination therapy may have potential utility against COVID-19.
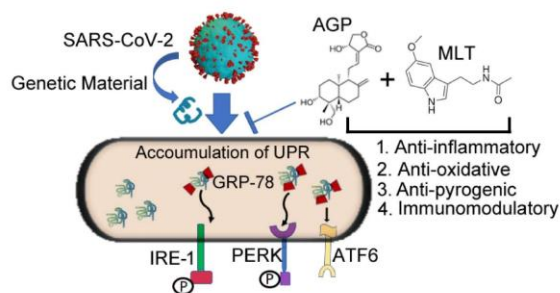
FIGURES

Figure 1. Schematic representation of the modulation of the UPR arms on SARS-CoV-2 infection illustrating the potential benefits of melatonin and andrographolide as an adjuvant use of melatonin and andrographolide. We postulated that genetic material transmitted from SARS-CoV-2 causes elevation of ER stress master regulator (GRP-78) and ER stress transducers IRE-1, PERK, ATF-6. The combined anti-inflammatory, anti-oxidative, anti-pyrogenic and immunomodulatory properties of andrographolide and melatonin could provide a useful adjuvant therapy for COVID-19 by altering ER stress signals.