

## News and Views

### The Case for Fludrocortisone + Hydrocortisone in Septic Shock

Administration of a combination of fludrocortisone and hydrocortisone reduced mortality by 12% among patients with septic shock compared to hydrocortisone alone, according to a study published in the *American Journal of Respiratory and Critical Care Medicine*.<sup>1</sup>

The objective of this study was to compare the effectiveness and safety of fludrocortisone + hydrocortisone versus hydrocortisone alone versus placebo/usual care in adult patients with septic shock. The researchers conducted a systematic review and Bayesian network meta-analysis of randomized trials published in peer-reviewed journals. All-cause mortality at the last follow-up was set as the primary outcome of the study. The reference treatment used for comparison was placebo/usual care.

Based on the analysis of 17 trials involving 7,688 patients, the combination of fludrocortisone + hydrocortisone demonstrated the lowest all-cause mortality at last follow-up, with a relative risk (RR) of 0.85 and a high probability (98.3%) of being superior, supported by moderate-certainty evidence. Hydrocortisone alone had a slightly higher RR of 0.97 and a lower probability (73.1%) of superiority, based on low-certainty evidence.

The authors note that the comparison between fludrocortisone + hydrocortisone and hydrocortisone alone relied primarily on indirect evidence, with only two trials providing direct evidence. However, the combination therapy still showed a 12% lower risk of all-cause mortality compared to hydrocortisone alone, with an RR of 0.88 and a 94.2% probability of superiority, supported by moderate-certainty evidence.

In adult septic shock patients, the combination of fludrocortisone + hydrocortisone was found to be associated with a lower risk of all-cause mortality at last follow-up compared to both placebo and hydrocortisone alone. However, it is important to note that owing to the paucity of head-to-head trials comparing fludrocortisone + hydrocortisone versus hydrocortisone alone; this network meta-analysis relied mainly on indirect evidence for this comparison, as per the authors. Although several sensitivity analyses and assessments were undertaken to ensure the robustness of our findings, it is crucial to consider these results

while also acknowledging the heterogeneity of the included trials.

Fludrocortisone is a very potent mineralocorticoid, while hydrocortisone has mineralocorticoid and glucocorticoid activity. The comparative activity of hydrocortisone to fludrocortisone is approximately 1 to 125-150; this ratio is mainly derived from the effects of hydrocortisone and fludrocortisone on sodium retention in the kidneys.

There is evidence to suggest that in patients with sepsis, the production of mineralocorticoids is impaired considerably more than the synthesis of glucocorticoids. This deficiency in mineralocorticoid synthesis has been found to be associated with a higher risk of sepsis-related mortality.<sup>2</sup>

Earlier studies have elucidated on the potential role of mineralocorticoids in septic shock.

There are different isoforms of the mineralocorticoid receptor. Some of these isoforms can bind to both glucocorticoids and mineralocorticoids, while others specifically bind to mineralocorticoids. The deactivation of glucocorticoids ensures that mineralocorticoids have a strong interaction with mineralocorticoid receptors. These receptors are also present in immune cells and when activated, they can enhance leukocyte adhesion, which can be beneficial in eradicating bacterial infections. Experimental sepsis studies have shown that mineralocorticoids, such as fludrocortisone, can reduce the levels of histamine, serotonin and bradykinin in the plasma, leading to a faster reversal of shock.<sup>2</sup>

Addition of fludrocortisone enhances the mineralocorticoid activity. By affecting salt and water balance in the body, mineralocorticoids may have a role in septic shock by restoring the effective blood volume through increased mineralocorticoid activity. On the other hand, glucocorticoids preferentially affect sugar metabolism and show sex hormone activities.<sup>3</sup>

These findings provide support for the beneficial effects of addition of fludrocortisone to hydrocortisone in lowering the risk of short-term mortality in these patients.

### References

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### Endometriosis and Pregnancy Outcomes

Pregnant women with stage III or IV endometriosis are likely to have a higher incidence of placenta previa compared to pregnant women with stage I or II endometriosis, suggests a study published in the *European Review for Medical and Pharmacological Sciences*.<sup>1</sup> But other pregnancy complications did not differ much in the two disease severity groups.

Through this retrospective study, Zhao-Zhen Liu, from the Dept. of Obstetrics and Gynecology at the College of Clinical Medicine for Obstetrics, Gynecology and Pediatrics at Fujian Medical University, China, and coauthors aimed to investigate the impact of endometriosis on pregnancy and assess any potential pregnancy complications and neonatal outcomes in patients with pregnancies complicated by endometriosis. Their goal was to contribute to a better understanding of the impact of endometriosis on pregnancy outcomes.

A total of 3,809 pregnant women who underwent cesarean section delivery at Fujian Maternity and Child Health Hospital in China between January 2014 and December 2020. Among them, 1,026 were diagnosed with endometriosis after the cesarean section, forming the endometriosis group. The control group consisted of 2,783 women without endometriosis.

The endometriosis group was further categorized into subgroups based on the disease severity; the first subgroup consisted of 882 subjects with stage I or II endometriosis, while the second subgroup comprised 144 parturients with stage III or IV endometriosis. During the study, general data of all patients and medical records of pregnancy complications and neonatal outcomes were collected and retrospectively analyzed. Age, gestational age, gestation and parity times were comparable between endometriosis and control groups.

Results showed no statistically significant differences in age, gestational age, gestation and parity times between all groups ( $p > 0.05$ ). However, the incidence of pre-eclampsia and placenta previa in the endometriosis

group was higher compared to the control group ( $p < 0.05$ ). No significant between-group differences were observed with regard to other pregnancy complications such as chronic hypertension with pregnancy, pre-eclampsia with chronic hypertension, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, gestational diabetes mellitus, pregestational diabetes mellitus, intrahepatic cholestasis of pregnancy, premature rupture of membranes and placental abruption.

When the two subgroups were analyzed, patients with more severe endometriosis, stage III/IV were found to have higher incidence of placenta previa compared to those with stage I/II endometriosis ( $p < 0.05$ ). Additionally, the amount of postpartum hemorrhage (1,000-1,500 mL) was significantly greater in the endometriosis group compared to the control group. However, there was no significant difference in the incidence of postpartum hemorrhage among patients with pregnancies complicated by endometriosis at different stages.

These findings provide valuable insights into the potential risks and complications associated with endometriosis during pregnancy and suggest that endometriosis may contribute to an increased risk of certain pregnancy complications. They show that in pregnant women, endometriosis is associated with an increased incidence of placenta previa, and this correlation is influenced by the severity of the disease. Additionally, pregnant women with endometriosis have higher rates of pre-eclampsia and postpartum hemorrhage compared to women without endometriosis. It is important to consider these factors when managing and providing care for pregnant women with endometriosis.

### Reference

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### Prognostic Factors in Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Long-term use of supplemental oxygen, the need for invasive mechanical ventilation upon admission, pre-exacerbation steroid use and increased neutrophils in bronchoalveolar lavage (BAL) are indicators of higher mortality risk in patients acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). These findings from a systematic review and meta-analysis were published in *Respiratory Medicine*.<sup>1</sup>

To understand the factors that contribute to mortality in patients with AE-IPF, researchers from Canada, USA, UK, Norway and Australia conducted a systematic

review and pairwise meta-analysis of factors associated with mortality in these patients. For this they searched databases such as Embase, Medline and CINAHL for studies that reported on the association between any prognostic factor and AE-IPF in adult patients. A total of 35 studies, involving over 18,000 patients, published between 1990 and 2022 were included in the analysis. Over two-thirds of them were from Japan with other participants from South Korea, Canada, China and the US. Their mean age ranged from 64.6 to 78.5 years and majorities were male.

Review of these studies revealed several factors related to the risk of death in patients with AE-IPF.

Long-term use of supplemental oxygen at baseline more than doubled the risk of death in patients with AE-IPF with adjusted hazard ratio (aHR) 2.52 with moderate certainty of evidence. Additionally, a diagnosis of IPF compared to non-IPF interstitial lung disease (ILD) was associated with an increased risk of death (aHR 2.19) with moderate certainty of evidence. Mortality was also increased in patients aged  $\geq 80$  years versus younger patients (aHR 2.98).

Radiographic factors associated with higher risk of death in these patients were also identified. These included: a diffuse pattern on high-resolution computed tomography (HRCT) (vs. non-diffuse pattern) with aHR of 2.61 (with moderate certainty) and a higher CT score (aHR 1.14) with low certainty.

Use of steroids before hospitalization for exacerbation increased the odds of mortality with aHR of 2.19. Patients with neutrophilia (% increase) in BAL during the exacerbation were at an increased risk of death with aHR of 1.02 (moderate certainty). Risk of mortality was higher among patients who needed invasive mechanical ventilation upon admission (aHR 3.74).<sup>2</sup>

This study has defined factors that adversely affect prognosis in patients with AE-IPF. Identification of these factors can therefore help clinicians to define clinical management and treatment decisions and potentially improve outcomes in these patients. Nevertheless, the authors have called for further studies “to validate additional prognostic factors to inform IPF management”.

## References

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## Common Household Cleaning Products and Asthma Control

Frequent use of household disinfectants and cleaning products in a week is strongly associated with uncontrolled asthma, says a study published in *The Journal of Allergy and Clinical Immunology: In Practice*. The risk increased with almost every day use.<sup>1,2</sup>

This study examined the impact of household disinfectants and cleaning products (HDCPs), including irritants and green products, sprays and disinfecting wipes and asthma control using 2018 data from the French Web-based NutriNet-Santé cohort. A standardized questionnaire was used to assess asthma control and the use of HDCPs at home. Factors such as sex, age, smoking status, body mass index (BMI) and educational level were considered. In the overall study population of 37,043 patients, the mean age was 47.5 years; three-fourth of them were women. In addition, 12.5% were current smokers, 32.2% were classified as overweight (BMI 25 kg/m<sup>2</sup>), and ~64% participants had completed at least 2 years of university education. Sixty-two percent reported using at least 1 HDCP every week.

Participants with current asthma and uncontrolled asthma tended to be younger, female, current smokers and overweight. Those with current asthma had higher education levels and those with uncontrolled asthma had lower educational status.

Based on the analysis conducted on 37,043 adults, it was found that greater weekly use of HDCPs was strongly associated with uncontrolled asthma.

Those who used irritants and green products almost daily (4-7 days/week) were at least twice more likely to have uncontrolled asthma with odds ratios (ORs) of 2.81 and 2.40, respectively (vs. those who used them for 1-3 days/week with ORs of 1.65 and 1.49, respectively). A similar association was noted with use of sprays (OR 2.69) (vs. 1.49 for 1-3 days/week use). Those who used disinfecting wipes were 3.5 times more likely to have poorly controlled asthma (OR 3.51) (vs. 2.2 for 1-3 days/week use). Notably, even when not used together with irritants and sprays, both disinfecting wipes (OR 1.99) and green products (OR 1.59) still showed statistically significant associations with uncontrolled asthma.

Subjects with overweight showed stronger association between use of irritants, sprays and green products and current asthma. Likewise, the association was also strong among participants who did not have any household help compared to those who had household help.

The use of irritants or sprays as household cleaning products are known to be associated with respiratory symptoms. Hence, green products and wipes are often used as alternatives to mitigate or minimize the potential respiratory risks while maintaining a clean and healthy household environment. By demonstrating an association between the weekly use of HDCPs, including green products or wipes and uncontrolled asthma, this study suggests that the use of HDCPs may have an impact on asthma symptoms and management.

This study draws attention to triggers other than the conventionally known ones such as upper respiratory infections, environmental allergens (like pollen, dust mite), cigarette smoke and air pollution. It is important for health practitioners to be aware of the impact of common household cleaning items on asthma and consider it when developing treatment plans for their patients to improve and maintain asthma control. While they may not entirely be preventable, they can be controlled for a good quality of life.

### References

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### Predicting Occurrence of Hypothyroidism in OSA Patients with Lymphocyte Count

A new study published in the journal *BMC Pulmonary Medicine* has suggested that the prevalence of hypothyroidism rises with increasing lymphocyte count in patients with obstructive sleep apnea (OSA).<sup>1</sup>

Xiaoyan Fang from the Dept. of Respiratory and Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin in China and colleagues conducted this retrospective study to evaluate the association between lymphocytes and hypothyroidism specifically in patients with OSA. The study participants underwent routine blood tests, including thyroid profile and nocturnal sleep monitoring. The researchers used logistic regression analysis to identify independent predictors of hypothyroidism in OSA patients. Additionally, they determined the cut-off level of lymphocyte count using a receiver operating characteristic (ROC) analysis to

determine the occurrence of hypothyroidism in these patients.

They selected 920 patients attending the Sleep Center at the Tianjin Medical University General Hospital. The prevalence of hypothyroidism was found to be 4.46% (n = 41), the prevalence in male patients was 3.4% and in female patients, it was 6.6%. Around 95.5% (n = 879) had normal thyroid function. The BMI of OSA patients with hypothyroidism was higher (34.78) than in controls (32.38). Epworth Sleepiness Scale (ESS) scores were significantly higher in OSA patients with hypothyroidism versus controls (10 vs. 6).

The researchers found that in the entire OSA population and male OSA patients, the lymphocyte percentage and lymphocyte count were significantly higher in the hypothyroid group compared to the control group. On subgroup analysis, the lymphocyte counts were markedly raised among OSA patients younger than 60 years old and those with mild to moderate OSA, the hypothyroid group had significantly higher lymphocyte counts compared to those with normal thyroid function.

The study identified lymphocyte count, ESS, and sex as independent predictors of hypothyroidism development in OSA patients. The ROC curve analysis indicated that the risk of hypothyroidism rose with increasing lymphocyte count in the overall patient population, with an optimal diagnostic cut-off point of  $2.5 \times 10^9/L$ .

This study demonstrates a correlation between the number of lymphocytes and the prevalence of hypothyroidism in patients with OSA, which includes subclinical hypothyroidism and not just overt. As the number of lymphocytes increased, the prevalence of hypothyroidism increased. A higher lymphocyte count therefore can be used as an independent predictor of the occurrence of hypothyroidism in this group of patients. The two conditions also share clinical features such as excessive sleepiness during the day, lethargy, obesity. Lymphocyte count is a simple and an easily available test and therefore can be undertaken to diagnose hypothyroidism in OSA patients followed by appropriate management resulting in better patient outcomes. Nevertheless, researchers advocate further research to corroborate their findings and to understand the mechanisms of this association.

### Reference

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