Hydrocortisone plus Fludrocortisone -- Promising rescue in septic Shock:

Septic shock is defined by a dysregulated host response to infection, resulting in life-threatening circulatory, cellular, and metabolic abnormalities. The short-term mortality is approximately 45-50%, and around half of survivors of sepsis may have subsequent long-term cognitive decline. Apart from early hemodynamic, respiratory resuscitation and appropriate antimicrobial treatments, there is no approved adjunct therapy for sepsis.

Experimental and clinical evidence suggests that sepsis is associated with a dysregulated response of the hypothalamic–pituitary–adrenal axis that may involve any of the steps from cortisol production to cortisol use by cells. A multicenter, double-blind, randomized trial published in NEJM (March 2018) concluded that combination of hydrocortisone and fludrocortisone decreases all-cause mortality rate in septic shock and decreases the time interval needed for weaning from ventilator and to achieve a SOFA score of less than 6.Hence, the administration of these drugs should not be uncommon in the management of septic shock.

Reference:N Engl J Med 2018; 378:809-818

Vitamin D deficiency increases Colorectal Cancer Risk

Vitamin D is regarded as the key vitamin for regulation of bone metabolism and homeostasis. It has a profound effect on the immune system and the intestinal barrier function. It's essential for regulatory actions in the gut, as it relates to proliferation and differentiation, intestinal barrier function, innate immunity and host response. Vitamin D expression declines in particular as it relates to late-stage colon cancer and it's absent in colorectal cancer metastasis.

The new study supports the idea that vitamin D deficiency makes a difference. Researchers pooled data from 17 study cohorts (5706 colorectal cancer patients and 7107 controls) to determine colorectal cancer risk at various ranges of vitamin D. They used the traditional measure for vitamin D deficiency of < 30 nmol/L. The threshold for sufficient bone health is around 50 to < 62.5 nmol/L. Vitamin D levels in this range were associated with a risk reduction for colorectal cancer of 19%, while those in the range of 87.5 to < 100 nmol/L were associated with a 27% risk reduction.However, there seemed to be a plateau effect at 100 nmol/L. It didn't mean that more was better forever. Nonetheless, it raises the bar for vitamin D supplementation in our patients.

Reference: Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts; published in Journal of National Cancer study: **https://doi.org/10.1093/jnci/djy087**

Elective Cesarean --Risk factor for an infant growing overweight

Elective cesarean delivery has been incriminated as a risk factor which doubles the chances of an infant becoming overweight at the age of 12 months, according to a prospective birth cohort study from Duke-NUS Medical School, Singapore, in their article published online November 21 in *JAMA Network Open,* which looked at outcomes of elective and emergency cesarean sections separately. In comparison, no significant association was found between overweight and emergency cesarean deliveries.

In an era when the elective cesarean deliveries are rising globally, it should be emphasized to discuss the potential long-term implications of elective cesarean delivery on child's metabolic outcome with patients who intend to have children.

Reference:JAMA Netw Open. 2018; 1(7):e185025. doi:10.1001/jamanetworkopen.2018.5025

Gilteritinib – New hope for Refractory Acute Myeloid Leukaemia

The US Food and Drug Administration (FDA) has approved Gilteritinib for the treatment of adult patients with FLT3 mutation-positive relapsed or refractory acute myeloid leukaemia (AML). Approval is based on an interim analysis of the ADMIRAL trial. FLT3 is the most frequently mutated gene that has been identified in AML, and FLT3 internal tandem duplication mutations are associated with high relapse rates, short remissions, and poor survival outcomes. Gilteritinib is a highly selective FLT3 TKI that has

demonstrated activity against FLT3 ITD mutations, and also inhibits FLT3 D835 mutations that can confer clinical resistance to other FLT3 inhibitors.

Reference: USFDA Approvals- 2018

Hormonal therapy- cause of treatment resistance in Breast Cancer

Metastatic breast cancer treated with hormonal therapy in view of ER positive status may acquire mutations in human epidermal growth factor receptor-2 (HER-2) and become treatment resistant. This suggests that even metastatic breast cancers evolve.This study was reported from Dana-Farber Cancer Institute and the Broad Institute and published in Nature Genetics. These HER2 mutations seem to be a mechanism of resistance to therapies that target the estrogen receptor, which explains the context in which they are acquired.

The researchers demonstrated in cell lines, and in one patient example, that the resistance acquired due to HER-2 mutation could be reversed by a combination of the hormone therapy Fulvestrant and the HER2 kinase inhibitor Neratinib.

Reference: Nature Genetics (2018). DOI: 10.1038/s41588-018-0287-5

Zoledronate – prevents fractures in osteopenic post-menopausal women

Most fractures in postmenopausal women occur in those with osteopenia.

I.R Reid et al conducted a double blind trial on post-menopausal women with age around 65 years. The results revealed significant reduction in non-vertebral and vertebral fractures in osteopenic women receiving Zoledronate injections as compared to those receiving placebo.

Reference: NEJM October (2018). DOI: 10.1056/NEJMoa1808082

Pantoperazole as good as placebo

Proton pump inhibitors like Pantoperazole are routinely used for prophylaxis against gastro-intestinal stress ulceration in ICU patients. A European multicentre, blinded trial was undertaken comparing patients in ICU (at risk of stress GI ulceration and bleed) receiving Pantoperazole with those receiving placebo; and primary outcome of 90 day mortality was observed. Results showed no statistically significant benefit in Pantoperazole Group over Placebo group with almost similar incidence of clinically significant event among the two groups.

Reference: N Engl J Med 2018; DOI: 10.1056/NEJMoa1714919