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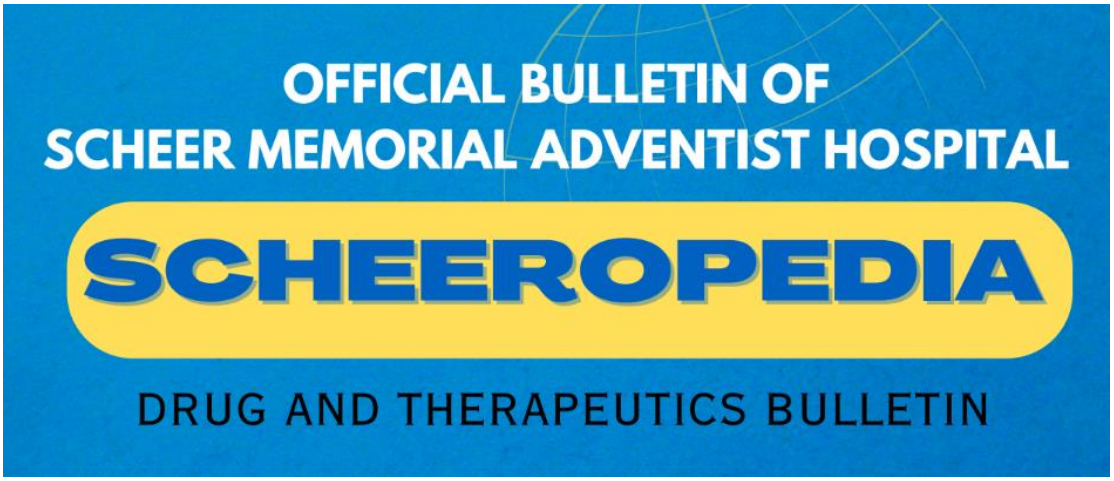

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Editorial

Getting Through the Scientific Odyssey: Overcoming Difficulties When Writing Scientific Papers

It seems appropriate to consider the obstacles the scientific and medical communities encounter when they attempt to publish their work as we say adieu to the struggles and victories of the previous year and welcome the start of a new one. It is not simple to spread knowledge through writing, and producing articles that are supported by science might be particularly difficult for medical professionals. For many years, the Drug and Therapeutic Bulletin has been a shining example of evidence-based medicine, giving researchers and practitioners a forum to discuss their discoveries, breakthroughs, and ideas. The constantly changing field of study presents one of the biggest obstacles for medical writers. As technology and methods continue to progress, it is becoming more and more necessary to stay up to date on the most recent breakthroughs. It can be difficult to find a unique perspective while upholding the standards of evidence-based practice, and authors must shift through a deluge of data in order to make a meaningful contribution.

Medical writers must learn the delicate dance of striking a balance between technical rigor and accessibility. Not only is it difficult to share knowledge, but it's also difficult to do so in a way that guarantees researchers, doctors, and the larger healthcare community understand it. There are numerous edits and iterations required along the difficult process from research findings to a final publication. It takes effort and commitment to create a narrative that not only conveys the findings but also tells a gripping story. The process of peer review is essential for preserving the integrity of scientific literature, but it also adds another level of scrutiny that calls for perseverance and a dedication to excellence. Cooperation is essential in the search for scientific truth. It may be gratifying and difficult to coordinate the efforts of interdisciplinary teams, each of which brings a different perspective to the table. Good communication and a common commitment to expanding medical knowledge are essential for navigating the range of viewpoints and levels of experience.

As we approach the start of a new year, let us recognize and honor the tenacity of our colleagues and their commitment and diligence are still evident in this forum for information sharing that helps to define healthcare's future. I hope that the Scheeropedia's pages will always serve as a showcase for the creativity and perseverance of our medical authors and this will eventually turn out to be the journey towards our hospital’s own medical journal.

Dr Anjan Khadka

Chief Editor

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LATEST RESEARCH UPDATES

1. Association between white blood cell count and adverse pregnancy outcomes: a retrospective cohort study from a tertiary hospital in China

Objectives This study aimed to clarify the relationship between white blood cell (WBC) and adverse pregnancy outcomes.

Design A total of 25 270 pregnant women underwent peripheral blood white blood cell count tests in the first, second and third trimesters. Adverse pregnancy outcomes were gestational hypertension, pre-eclampsia, gestational diabetes mellitus, preterm birth, low birth weight, caesarean delivery, macrosomia and fetal distress. Due to acute infectious disease or other diseases, 1127 were excluded.

Setting: Minhang Hospital, China.

Participants: A total of 24 143 pregnant women were included in this study.

Primary and secondary outcome measures: The primary outcome was the adverse pregnancy outcomes.

Results: For the 24 143 participants, we calculated adjusted ORs for adverse pregnancy outcomes associated with an increased WBC count. For gestational hypertension, the ORs were 1.18 (95% CI, 1.05 to 1.24) in the first trimester and 1.10 (1.06 to 1.13) in the second trimester; for pre-eclampsia, ORs were 1.14 (95% CI, 1.47 to 1.64) in the first trimester and 1.10 (1.05 to 1.16) in the second trimester; for gestational diabetes mellitus, ORs were 1.06 (95% CI, 1.00 to 1.13) in the first trimester and 1.10 (1.04 to 1.16) in the second trimester; for preterm birth, ORs were 1.12 (95% CI, 1.06 to 1.18) in the first trimester, 1.10 (1.06 to 1.13) in the second trimester and 1.12 (1.09 to 1.15) in the third trimester; for low birth weight, ORs were 1.09 (95% CI, 1.02 to 1.17) in the first trimester, 1.03 (0.99 to 1.08) in the second trimester and 1.12 (1.08 to 1.16) in the third trimester. Significant associations were not observed obviously for caesarean delivery, macrosomia and fetal distress.

Conclusions: Our results indicate strong, continuous associations of maternal WBC count with increased risks of adverse pregnancy outcomes.

Further read: Zhang Y, Qian Y, Liu C, Fan X, Li X, Song Y, et al. Association between white blood cell count and adverse pregnancy outcomes: a retrospective cohort study from a tertiary hospital in China. BMJ open. 2023 Nov 1;13(11):e072633. [https://bmjopen.bmj.com/content/13/11/e072633.abstract]

2. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes 2andomized trial

Background: The CLEAR Outcomes trial demonstrated that bempedoic acid reduced the risk of major adverse cardiovascular events among statin-intolerant patients at high cardiovascular risk. In this prespecified analysis, our dual aims were to evaluate the cardiovascular benefits of bempedoic acid, an ATP-citrate lyase inhibitor, in individuals with diabetes, and to evaluate the risk of new-onset diabetes and HbA_{1c} among those without diabetes in the CLEAR Outcomes trial.

Methods: CLEAR Outcomes was a 2andomized, double-blind, placebo-controlled trial conducted across 1250 primary care and outpatient sites in 32 countries. Patients with or without cardiovascular disease who were unwilling or unable to take guideline-recommended doses of statins and an LDL cholesterol of 2·59 mmol/L or more were randomly assigned (1:1) in a double-blinded manner to either bempedoic acid 180 mg once per day or placebo. In this prespecified analysis, the efficacy endpoint was a time-to-event analysis of four-component major adverse cardiovascular event (MACE-4), which is the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary 2andomized22n2ion, using the intention-to-treat population stratified by baseline glycaemia status.

Findings: Between Dec 22, 2016, and Nov 7, 2022, 13 970 patients were screened and randomly assigned; 6373 (45·6%) with diabetes, 5796 (41·5%) with prediabetes, and 1801 (12·9%) with normoglycaemia. Over a median of 3·4 years follow up, patients with diabetes had significant relative and absolute cardiovascular risk reductions in MACE-4 endpoints with bempedoic acid (HR 0·83; 95% CI 0·72–0·95; absolute risk reduction of 2·4%) compared to placebo, with no statistical evidence of effect modification across glycaemic strata (interaction p=0·42). The proportion of patients who developed new-onset diabetes were similar between the bempedoic acid and placebo groups, with 429 of 3848 (11·1%) with bempedoic acid versus 433 of 3749 (11·5%) with placebo (HR 0·95; 95% CI 0·83–1·09). HbA_{1c} concentrations at month 12 and the end of the study were similar between 2andomized groups in patients who had prediabetes and normoglycaemia. Placebo-corrected LDL cholesterol concentrations and high-sensitivity C-reactive protein at 6 months were reduced in each glycaemic stratum.

Interpretation: Among patients with diabetes, bempedoic acid reduces LDL cholesterol and high-sensitivity C-reactive protein and risk of cardiovascular events. Patients without diabetes had no increase in new-onset diabetes or worsening HbA_{1c} with bempedoic acid. The efficacy and cardiometabolic safety profile of bempedoic acid makes it a clinical option for those with and without diabetes.

Further read: Ray KK, Nicholls SJ, Li N, Louie MJ, Brennan D, Lincoff AM, et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes 2andomized trial. The Lancet Diabetes & Endocrinology. 2023 Dec 4.
[https://www.thelancet.com/journals/landia/article/PIIS2213-8587(23)00316-9/fulltext]

3. Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a 3andomized3, double-blind, 3andomized, placebo-controlled trial

Background: Vitamin D supplementation has been shown to increase total hip areal bone mineral density in healthy children and adolescents. The study aimed to investigate whether supplementing schoolchildren living in Mongolia with weekly vitamin D_3 for 3 years affected fracture risk.

Methods: It is a 3andomized3, double-blind, 3andomized, placebo-controlled trial across 18 public schools in Ulaanbaatar, Mongolia. Schoolchildren were eligible if they were aged 6–13 years at screening, had a negative QuantiFERON-TB Gold In-tube assay (QFT) result, were not hypersensitive to vitamin D or immunocompromised, did not use vitamin D supplements, did not have clinical signs of rickets, and had no intention of leaving Ulaanbaatar within 3 years. Participants were randomly assigned (1:1) to receive either vitamin D (oral dose of 14 000 international units [IU] vitamin D_3, once per week) or placebo for 3 years using permuted block 3andomized33n stratified by school of attendance. Participants, care providers, and all trial staff were masked to group assignment during the intervention. Prespecified secondary outcomes were incidence of fractures and adverse events, ascertained using questionnaires. The fracture and safety analyses included participants who completed at least one follow-up fracture questionnaire. Study estimated adjusted risk ratios (RRs) and 95% Cis using 3andomized3 linear models with binomial distribution and a log link function with adjustment for school of attendance. The trial is registered with ClinicalTrials.gov, NCT02276755, and the intervention ended in May, 2019.

Findings: Between Sept 2, 2015, and March 20, 2017, 11 475 children were invited to participate in the study and 8851 were recruited and randomly assigned to receive either vitamin D (n=4418) or placebo (n=4433). 8348 participants were included in the fracture and safety analyses (4176 [94·5%] in the vitamin D group and 4172 [94·1%] in the placebo group). Of these, 4125 (49·4%) were female, 4223 (50·6%) were male, and 7701 (92·2%) were of Khalkh ancestry. Median age was 9·2 years (IQR 8·0–10·7) and 7975 (95·5%) participants had baseline serum 25-hydroxyvitamin D concentrations less than 50 nmol/L. During a median follow-up of 3·0 years (IQR 2·9–3·1), 268 (6·4%) participants in the vitamin D group and 253 (6·1%) in the placebo group reported one or more fractures (adjusted RR 1·10, 95% CI 0·93–1·29; p=0·27). Incidence of adverse events did not differ between study groups.

Interpretation: Oral vitamin D supplementation at a dose of 14 000 IU/week for 3 years was safe, but did not influence fracture risk in schoolchildren living in Mongolia who had a high baseline prevalence of vitamin D deficiency.

Further read: Ganmaa D, Khudyakov P, Buyanjargal U, Tserenkhuu E, Erdenenbaatar S, Achtai CE, et al. Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a 3andomized3, double-blind, randomised, placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2024 Jan 1;12(1):29-38. [https://www.thelancet.com/journals/landia/article/PIIS2213-8587(23)00317-0/fulltext]

4. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial

Background: The EMPA-KIDNEY trial showed that empagliflozin reduced the risk of the primary composite outcome of kidney disease progression or cardiovascular death in patients with chronic kidney disease mainly through slowing progression. We aimed to assess how effects of empagliflozin might differ by primary kidney disease across its broad population.

Methods: EMPA-KIDNEY, a randomised, controlled, phase 3 trial, was conducted at 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the UK, and the USA). Patients were eligible if their estimated glomerular filtration rate (eGFR) was 20 to less than 45 mL/min per 1·73 m^2, or 45 to less than 90 mL/min per 1·73 m^2 with a urinary albumin-to-creatinine ratio (uACR) of 200 mg/g or higher at screening. They were randomly assigned (1:1) to 10 mg oral empagliflozin once daily or matching placebo. Effects on kidney disease progression (defined as a sustained ≥40% eGFR decline from randomisation, end-stage kidney disease, a sustained eGFR below 10 mL/min per 1·73 m^2, or death from kidney failure) were assessed using prespecified Cox models, and eGFR slope analyses used shared parameter models. Subgroup comparisons were performed by including relevant interaction terms in models. EMPA-KIDNEY is registered with ClinicalTrials.gov, NCT03594110.

Findings: Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and followed up for a median of 2·0 years (IQR 1·5–2·4). Prespecified subgroupings by primary kidney disease included 2057 (31·1%) participants with diabetic kidney disease, 1669 (25·3%) with glomerular disease, 1445 (21·9%) with hypertensive or renovascular disease, and 1438 (21·8%) with other or unknown causes. Kidney disease progression occurred in 384 (11·6%) of 3304 patients in the empagliflozin group and 504 (15·2%) of 3305 patients in the placebo group (hazard ratio 0·71 [95% CI 0·62–0·81]), with no evidence that the relative effect size varied significantly by primary kidney disease ($p_{heterogeneity}$=0·62). The between-group difference in chronic eGFR slopes (ie, from 2 months to final follow-up) was 1·37 mL/min per 1·73 m^2 per year (95% CI 1·16–1·59), representing a 50% (42–58) reduction in the rate of chronic eGFR decline. This relative effect of empagliflozin on chronic eGFR slope was similar in analyses by different primary kidney diseases, including in explorations by type of glomerular disease and diabetes (p values for heterogeneity all >0·1).

Interpretation: In a broad range of patients with chronic kidney disease at risk of progression, including a wide range of non-diabetic causes of chronic kidney disease, empagliflozin reduced risk of kidney disease progression. Relative effect sizes were broadly similar irrespective of the cause of primary kidney disease, suggesting that SGLT2 inhibitors should be part of a standard of care to minimise risk of kidney failure in chronic kidney disease.

Further read: Abat S, Abd Rahman R, Cader RA, Hafidz MA, Wahab MA, Abdullah NK, et al. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. The Lancet Diabetes & Endocrinology. 2023 Dec 4. [https://www.thelancet.com/journals/landia/article/PIIS2213-8587(23)00322-4/fulltext]

5. Intrarectal injections of botulinum toxin versus placebo for the treatment of urge faecal incontinence in adults (FI-Toxin): a double-blind, multicentre, randomised, controlled phase 3 study

Background: Non-randomised studies assessing intrarectal botulinum toxin type A (BoNTA) injections for faecal incontinence are promising. We aimed to evaluate the efficacy of BoNTA for the treatment of faecal incontinence in a randomised study.

Methods: In this randomised, double-blind, placebo-controlled study, we included adult patients who had at least one urgency or faecal incontinence episode per week for at least 3 months and who had experienced a failure of conservative or surgical treatment from eight French specialist hospital units with the skills to manage patients with faecal incontinence. Patients were randomly assigned (1:1) by a central web form to receive intrarectal submucosal injections of either 200 units of BoNTA (Botox; Allergan, Irvine, CA, USA; BoNTA group) or an equivalent volume of saline (placebo group), stratified by Cleveland Clinic Severity scores (CCS score; ≥12 or <12). Patients, investigators, study site staff, and sponsor personnel were masked to treatment allocation up to the 6-month visit. The primary endpoint was the number of episodes of faecal incontinence and urgency per day assessed using 21-day patient bowel diaries 3 months after the treatment. The primary analysis was performed using a modified intention-to-treat (mITT) approach (ie, in all the randomised patients who had received a treatment) with adjustment for baseline faecal incontinence and urgency episodes. This trial is registered with ClinicalTrials.gov, number NCT02414425.

Findings: Between Nov 25, 2015, and Nov 25, 2020, we randomly assigned 200 patients to receive either BoNTA (n=100) or placebo (n=100) injections. Due to withdrawals before the injections, 96 patients were included in the BoNTA group and 95 patients were included in the placebo group (mITT analysis). The mean number of faecal incontinence and urgency episodes per day in the BoNTA group decreased from 1·9 (SD 2·2) at baseline to 0·8 (1·8) at 3 months after the injections, and from 1·4 (1·1) to 1·0 (1·0) in the placebo group, with a baseline-adjusted mean group difference at 3 months estimated at −0·51 (95% CI −0·80 to −0·21, p=0·0008). No serious treatment-related adverse events were reported in the trial. The most frequently reported non-serious adverse event (treatment related or not) following the BoNTA or placebo injections was constipation (reported in 68 [40%] of 169 patients who received the BoNTA injections and 38 [40%] of 95 patients who received placebo injections).

Interpretation: BoNTA injections are an efficacious treatment for urge faecal incontinence. Further research will define the optimum selection criteria, dose, site of injection, re-injection frequency, and long-term results.

Further read: Leroi AM, Queralto M, Zerbib F, Siproudhis L, Vitton V, Amarenco G, et al. Intrarectal injections of botulinum toxin versus placebo for the treatment of urge faecal incontinence in adults (FI-Toxin): a double-blind, multicentre, randomised, controlled phase 3 study. The Lancet Gastroenterology & Hepatology. 2023 Dec 15. [https://www.thelancet.com/journals/langas/article/PIIS2468-1253(23)00332-1/fulltext]

A cardiac twin: a case report

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Abstract

Twin reversed arterial perfusion sequence refers to a rare, unique complication of mono-chorionic twin pregnancy. It arises when the cardiac system of one twin does the work of supplying blood for both twins. The twin supplying the blood is known as “pump” twin. The other twin is known as the “acardiac twin”. This case report presents an antenatally diagnosed mono-chorionic twin pregnancy, resulting in preterm delivery of a healthy, normal twin along with an acardiac co-twin.

Keywords: acardiac twin, mono-chorionic twin, multiple pregnancy

Introduction

Multiple pregnancy accounts for 1.5% of all pregnancies, with approximate perinatal morbidity and mortality of 10%. Twin reversed arterial perfusion (TRAP) occurs in 1 in 35000 pregnancies.[1] The first cases of acardia were reported by Benedetti in 1533 and Benedictus in 1539, and later by Geoffrey in 1836. Five hundred cases have been reported since then. In Nepal, in the past 10 years, two cases of acardia has been reported, one in Kathmandu Medical College in 2014 and another in Janaki Medical College in 2015.[2,3] One in every 100 monozygotic twin pregnancies and one in every 35,000 pregnancies overall are affected with acardiac twinning. When there is an acardiac twin, both the acardiac sibling and the normal (or "pump") twin need to have circulation. The acardiac twin and the normal twin can have nearly identical sizes. Preterm delivery, maternal hydramnios, and pump-twin congestive heart failure are the main perinatal issues linked to acardiac twinning.[4,5]

It has been hypothesized that the TRAP sequence is caused by a large artery to artery placental shunt. Within the single shared placenta, arterial perfusion pressure of the donor twin exceeds that in the recipient twin. The recipient twin receives reverse blood flow of deoxygenated arterial blood from its co-twin. A study done in 2007 on efficacy of radiofrequency ablation in TRAP syndrome showed more than 90% survival of the MCDA pregnancies complicated by TRAP.[5] However, due to limited cases and experience on MCMA Twin, efficacy in this group is not known. Here we are presenting a case of TRAP sequence, which created a considerable management dilemma.

Case presentation

25 years old G2P1L1 at 8 weeks of gestation presented to Obstetric OPD with complaints of Amenorrhea since 2 months. Routine investigations were done. USG (Dating Scan) showed single pregnancy with gestational age of 8 weeks. At 20 weeks, the patient had an anomaly scan done in Paropakar hospital which showed a MCDA twin pregnancy, Twin 1- IUFD with fetal generalized subcutaneous edema. Twin 2- live intrauterine fetus at 20 weeks of gestation. D-dimer and coagulation profile was checked which was normal. At 32 weeks, she was advised for a USG in Seer Imaging centre (Banepa) which showed – two intrauterine fetuses, one with no cardiac activity and other live fetus with regular cardiac activities corresponding to 33 weeks 2 days of gestation. After this, she was admitted with diagnosis of G2P1L1 at 33+1 weeks of gestation with monochorionic monoamniotic twin pregnancy with one twin IUFD. She was monitored regularly and 2 doses of Dexamethasone were completed. D-dimer was checked which was normal and coagulation profile was done in regular interval and was planned for Elective LSCS at 34+1 weeks of gestation. Twin 1- preterm female baby was born with birth weight of 2200 grams with Apgar score of 8/10 and 9/10. She was healthy and was given by mother's side. Twin 2- weighed 1500 grams, upper portion contained soft globular mass, head and upper extremities were absent, external genitalia female type but poorly developed. Autopsy revealed absence of fetal heart. She was discharged on 3rd POD with diagnosis of 3rd POD following elective LSCS for G2P1L1 at 34+1 WOG with MCMA Twin pregnancy with Acardiac twin (Twin reversed arterial perfusion sequence).

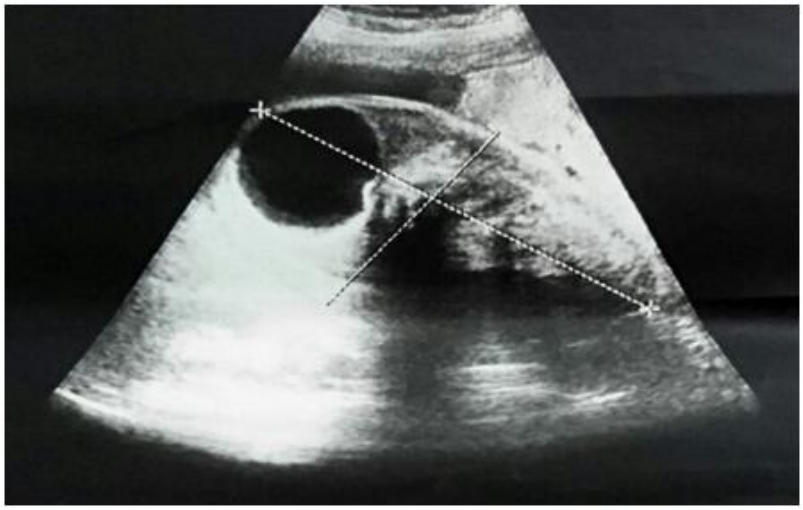

Figure 1 A large hypo-hetero-echoic mass (the amorphic fetus) without heart activity and with internal cystic calcification in ultrasound.

Figure 2. The normal baby

Figure 3. The acardiac twin without well-defined head and limbs.

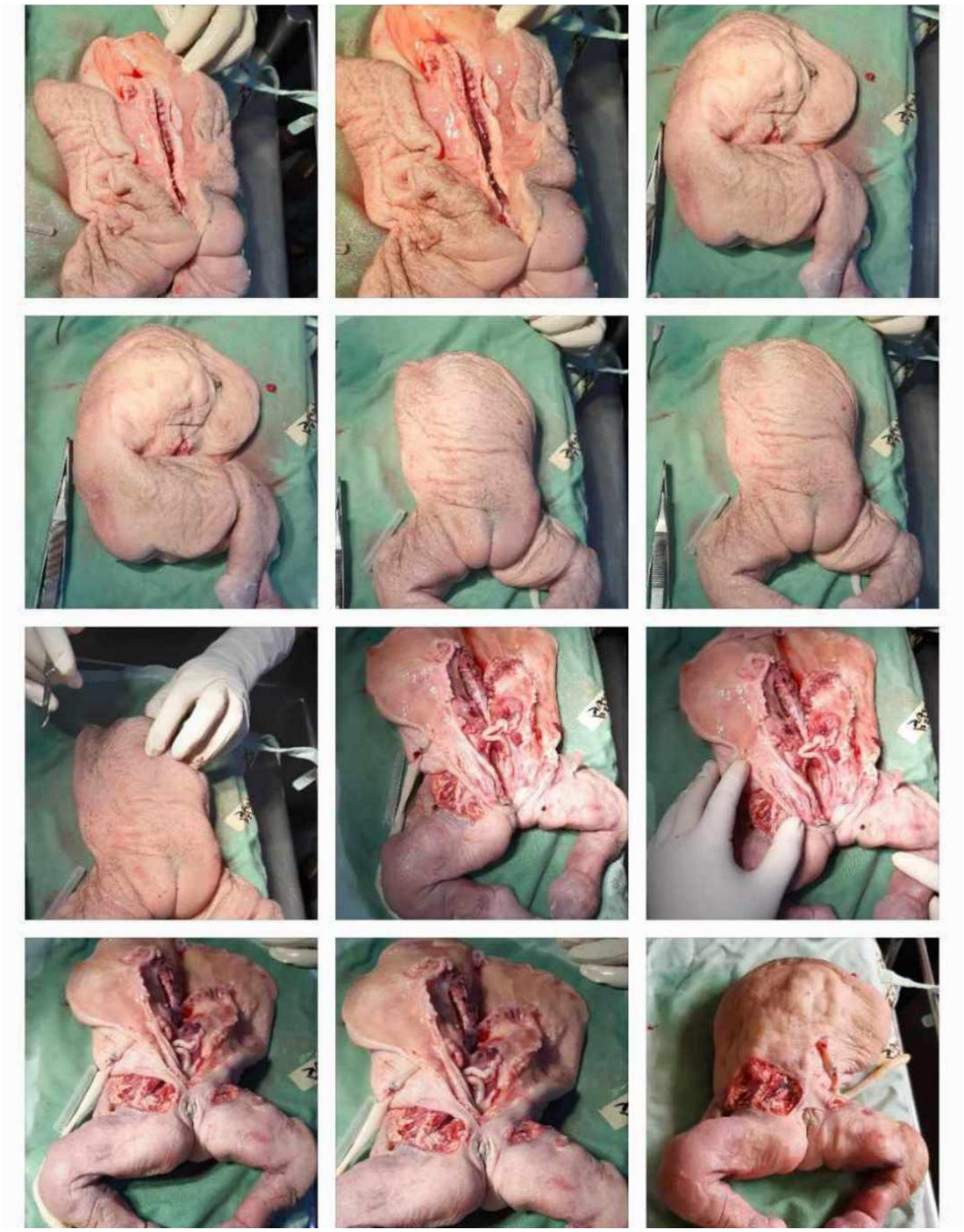

Figure 4. Acardiac twin (Autopsy)

Discussion

Acardiac twinning is a rare congenital anomaly characterized by formation of a malformed fetus with an absent or rudimentary (but nonfunctional) heart. A variety of acardiac twins have been described based on the degree of cephalic and truncal maldevelopment.[6] The *acardiac-acephalus* fetus has no cephalic development, while an *acardius-anceps* fetus has some cranial structures and/or neural tissue development. The *acardius-acormus* fetus has cephalic structures with limited or no truncal development.[7] The fourth type, the *acardius-amorphus* fetus, has the most severe malformation and lacks all cephalic and truncal differentiation. The acardiac twin, otherwise destined to end in an early spontaneous abortion, continues to grow because of mono-chorionic vascular anastomoses to a normal co-twin.[8] Antenatal diagnosis by ultrasound of an acardiac fetus coexisting with a normal co-twin is fairly straight forward. The only other entity in the differential diagnosis is an intrauterine fetal demise of one twin. The twin with cardiac activity may be hydropic or malformed in 9% of cases. This twin is often at high risk for congestive cardiac failure due to increased cardiovascular demand, resulting in preterm delivery. Perinatal mortality for the pump twin has been estimated to be up to 55%, while it is usually fatal for the acardiac twin.[9]

Radio-frequency ablation is done in cases where gestational age is more than 16 weeks. Procedure involves insertion of small needle into the uterus.[10] The needle contains sharp prongs that disperse heat energy of radio frequency. The heat energy is used to seal the feeding vessels supplying blood to the acardiac twin. A study done in 2007 on efficacy of radiofrequency ablation in TRAP syndrome showed more than 90% survival of the MCDA pregnancies complicated by TRAP.[11] However, due to limited cases and experience on MCMA Twin , efficacy in this group is not known. In cases where the gestational age is less than 16 weeks, bipolar coagulation can be recommended.[12] This procedure seals off a portion of the acardiac twin’s umbilical cord near the placenta. Due to lack of study and research, the efficacy of this procedure is not known. The healthy twin has more than a 90 percent chance of good outcome. The vestiges of the acardiac twin remains in the womb until delivery. Most women go on to have a normal delivery and a healthy baby.

Conclusion

This case demonstrates the importance of correct early diagnosis of acardiac twining to avoid later complications. Referring every twin pregnancy for a detailed early ultrasound to a specialized center, can avoid diagnosis and therapeutic difficulties later in the pregnancy. Conservative treatment is best suited for salvation of the pump twin when the acardiac twin is less than one fourth the weight of the pump twin and there are no signs of impending heart failure. Invasive intervention is justified when the acardiac twin exceeds 70% of that of the pump twin; however, the prognosis appears to be poor.

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Pulmonary Thromboembolism in COPD: The Silent killer

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Introduction:

GOLD 2023 defines Chronic Obstructive Pulmonary Disease (COPD) as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[1] Chronic Obstructive Pulmonary Disease (COPD) exerts a significant clinical, social and economic burden globally. The global prevalence of COPD oscillates around 12% of the general population. COPD currently ranks as the 3rd cause of mortality in the world (responsible for 3 million deaths), just behind CVDs.[2]

Epidemiology of COPD and Pulmonary Thromboembolism:

COPD has multiple extrapulmonary manifestations including widespread systemic inflammation, osteoporosis and musculoskeletal degeneration, coronary artery disease and increased risk of venous thromboembolism (VTE). Pulmonary thromboembolism (PE), in particular, is a dreaded and often underdiagnosed entity causing significant mortality and morbidity among COPD patients. COPD patients are thought at increased risk for venous thromboembolism (VTE) because of immobilization, heightened systemic inflammation, cigarette smoking, and venous stasis.[3] Postmortem studies in COPD have found pulmonary embolism (PE) in 28%-51% of cases.[4] PE is diagnosed by computed tomography (CT) angiography in 25% of individuals presenting with an unknown etiology for a COPD exacerbation.[5] VTE in COPD has prognostic implications. Prevalence of VTE in COPD has direct correlation with mortality and need for mechanical ventilation. One study found significantly higher 1-year mortality in COPD exacerbation with VTE (61.9% vs. 31.8%, p=0.013).[6] Another study showed increased duration of hospitalization and need for mechanical ventilation.[7]

A large cohort of unselected COPD patients showed that a history of VTE was associated with higher oxygen use, a lower 6-minute walk distance, a worse quality of life, a higher frequency of

exacerbations, and a higher smoking history. Additionally, those with a history of VTE were older, heavier, and more likely to have multiple medical comorbidities. These findings were reported in a retrospective cross-sectional analysis comparing smokers with worse airflow obstruction to nonsmoking controls and smokers with no or mild airflow.[8] The COPD patients were older (mean age 68 vs. 63 years), and had a higher frequency of heart failure (35.5% vs. 12.9%), and immobility (53.5% vs. 43.3%, all $p<0.0001$) compared to those without COPD.[8] The COPD individuals were more likely to die in the hospital and within 30 days of the VTE diagnosis.[8] Tillebrand et al found that in 25% of 211 patients with severe COPD exacerbations without an identifiable cause, the exacerbations were actually related to PEs.[5]

COPD in Nepal and local scenario of VTE/PE in COPD:

COPD is the most prevalent non-communicable diseases (NCDs) in Nepal, with 12% prevalence in adults.[9] In 2016, nearly one million Nepalese people were suffering from COPD, twice as many as in 1990.[10] Although a large-scale study on VTE and PE among COPD patients in Nepal is lacking, we can safely assume that the prevalence of VTE and PE is fairly high. It is a sad fact that often such catastrophic events are undiagnosed, underdiagnosed and unreported. Looking at the number of COPD patients who die in the community and present as dead-on arrival to the hospital with history of sudden collapse, we can assume that many of these patients have a diagnosis of VTE/PE including cerebrovascular accidents (CVA) and acute coronary events.

Management of VTE/PE in COPD:

Acute PE in patients with Acute Exacerbation of COPD (AE of COPD) is usually difficult to diagnose clinically because the clinical manifestations of these two diseases are often similar.[11] PE manifests as shortness of breath, chest tightness, chest pain, and hemoptysis, and is often accompanied by hemodynamic instability such as hypotension and hypoxia.[12] COPD patients with PE are less likely to develop cough, dyspnea, and syncope, whereas COPD patients who are prone to developing PE complications are often associated with lower extremities thrombosis.[13] In patients with AECOPD of unknown cause, pleural chest pain and heart failure are more strongly associated with PE, while symptoms of respiratory infection are less frequent.[14] Patients with AECOPD combined with VTE had higher D-dimer but lower hemoglobin levels than those without VTE.[15] The eosinophil level can be used as a biomarker to predict the risk of all-cause mortality in hospitalized patients with COPD exacerbation, and thromboembolism occurs

relatively commonly in patients with hypereosinophilic syndrome.[16] Eosinophilia can lead to multiple arterial and venous thromboses.[17] Catalytic cytotoxic proteins found in eosinophils, such as platelet-activating factor and eosinophilic peroxidase, cause and intensify inflammatory reactions, harm cells, encourage blood coagulation, and cause tissue damage. In addition, eosinophil cells can store tissue factors (TFs), which are believed to be the main initiator of blood clotting.[18] Glucocorticoid provided effective short-term control of hypereosinophilia to delay thrombosis.[17] The symptoms and signs of PE are nonspecific. Patients who experience dyspnea, chest discomfort, syncope, or hemoptysis—symptoms that characterize most COPD cases—should be closely watched for the possibility of PE. PE, however, can occasionally be identified while a patient is being examined for another illness or may present with no symptoms at all. Elevated D-dimer can only be used to rule out a diagnosis; it does not confirm the diagnosis. Acute PE can be excluded if D-dimer <500 μg/L. By using the D-dimer test in conjunction with the Simplified Geneva Score pre-test, diagnostic accuracy can be increased.[19] Studies have also shown that albumin (P = 0.0002) and RDW (P = 0.0446) significantly correlates with the occurrence of acute PE.[20] The combined diagnosis of albumin and RDW had the highest sensitivity and specificity, and the threshold was ≤3 g/dL, and >14 g/dL, respectively. End-tidal carbon dioxide (ETCO2) is also a meaningful indicator for the diagnosis of PE. When PE is diagnosed with a cut-off value of 34 mmHg, PE can be appropriately and reliably excluded when combined with clinical likelihood.[21] The "gold standard" for diagnosis is selective pulmonary angiography, while computed tomography (CT) pulmonary angiography is the recommended imaging technique for suspected PE. Direct diagnosis is possible through indications that correspond to deficiencies in the filling of the pulmonary arteries; indirect diagnosis is possible through signs such wedge-shaped pulmonary fields, banded densities or discoid pulmonary opacities, dilatation of the central pulmonary artery, and decreased or nonexistent distal vascular branches. The other modality like ventilation/perfusion single-photon emission computed tompography (V/Q SPECT) can be used as well which is useful for diagnosing both acute and chronic PE, and can be diagnosed when more than one subsegment shows V/Q mismatches representing anatomic lung units.[22]

The cornerstone of PE treatment is anticoagulation, which not only successfully inhibits thrombus formation and relapse but also has the ability to facilitate the fibrinolytic system's disintegration, which breaks down blood clots. Anticoagulant medication should be initiated as

soon as acute PE is clearly diagnosed. Currently, the first-line treatment for PE is direct oral anticoagulant (DOAC), which can also be used to treat PE and COPD together.[23] In the acute phase of high-risk PE with hemodynamic instability, unfractionated heparin (UFH) anticoagulation, including intravenous injection and systemic thrombolysis, should be used right away. One surgical option in the event of thrombolysis failure or contraindication is pulmonary embolectomy.[24] According to a study by Hara et al., DOAC should be administered following a single intravenous injection of UFH to high-risk PE patients with large thrombus. According to the findings, patients had lower hospital stay duration and a higher rate of pulmonary artery thrombosis reduction at three to six months following treatment than the patients in the traditional treatment group.[25] For patients with high risk of PE, inferior vena cava (IVC) filter implantation is an effective therapy option. In a multi-center retrospective analysis, 440,370 hemodynamically stable AECOPD patients complicated by PE were included and the findings indicated that IVC therapy can lower the absolute risk of death in patients over 50 by 2.1%.The death rate for those over 80 years of age fell from 14.4% to 9.1%.[26]

Conclusion:

When PE is added to AECOPD patients, the mortality rate rises and PE is thought to be an independent risk factor for a bad prognosis. However, PE is more likely to be misdiagnosed or disregarded in COPD patients due to comparable clinical symptoms. Consequently, early anticoagulant therapy becomes crucial to the management of AECOPD patients in order to prevent thrombosis. Oral anticoagulants have been utilized extensively in the treatment of COPD exacerbated by PE in recent years. There should be a high index of suspicion for VTE/PE in COPD patients admitted with acute exacerbations and there should be no delay in diagnosis. After the diagnosis of PE in COPD patients is confirmed, immediate treatment with anticoagulants should be commenced. More research and resources are required to address VTE/PE in COPD patients, particularly in low- and middle-income nations like our own where the disease is incredibly and tragically common.

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Antimicrobial stewardship: The necessity of time

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Introduction

Numerous approaches have been used to conceptualize antimicrobial stewardship, such as a program, an ethic, a philosophy, or a collection of coordinated interventions. The word "stewardship" has its roots in everyday deeds that are frequently complex: but coherent, set of maneuvers carried out to overcome an enemy.[1] The word "strategic" derives from the Greek word "strategos," which refers to a broad yet well-coordinated series of actions used to defeat an opponent. Those who translate strategy into operations are responsible for particular sets of maneuvers, or sorts of intervention. In addition, the acts run the risk of conflicting with one another if they lack coherence.[1,2]

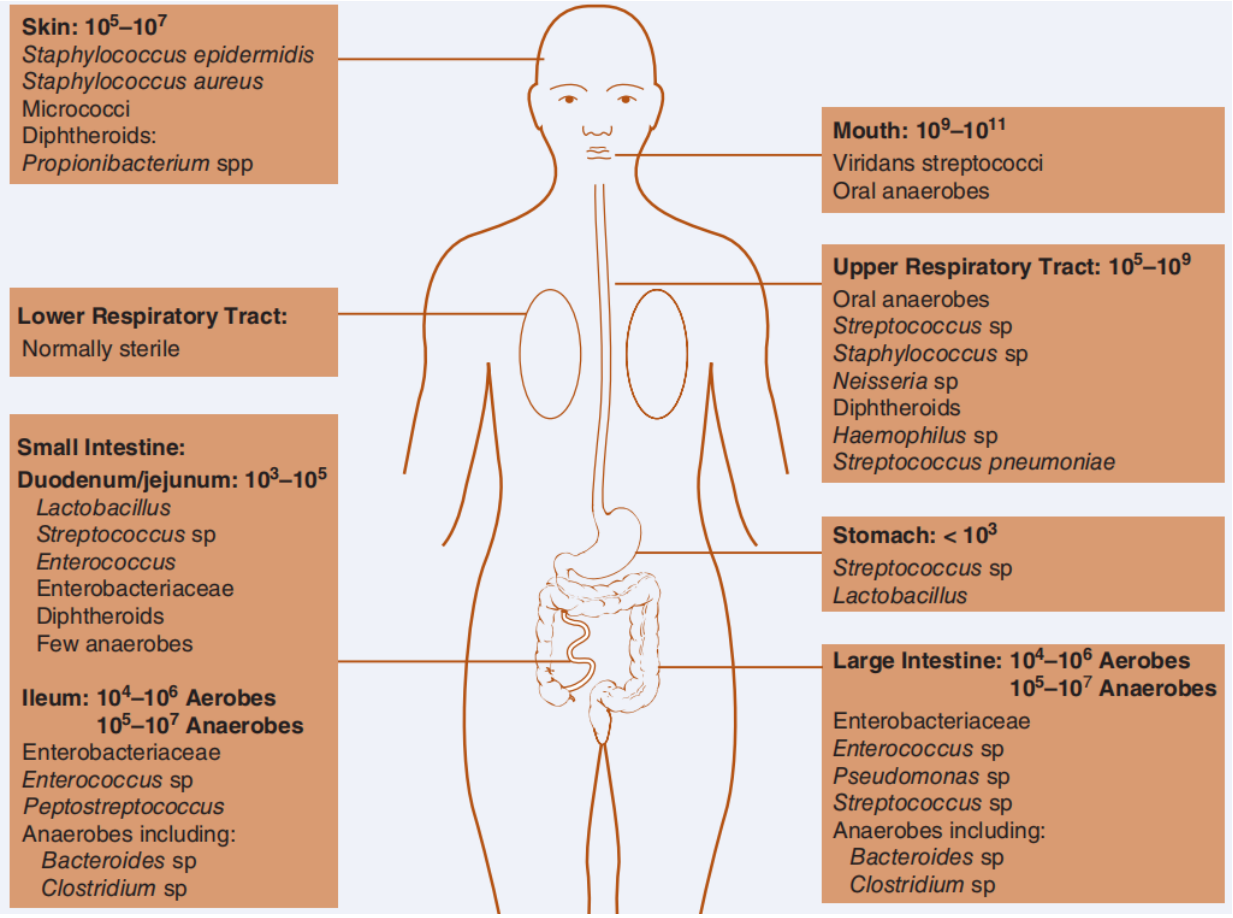
Antibiotic stewardship is the effort to[2]:

- measure antibiotic prescribing,
- improve antibiotic prescribing so that antibiotics are only prescribed and used when needed,
- ensure prompt initiation of the right antibiotics when they are needed, and
- ensure that the right drug, dose, and duration are selected.

Antimicrobial resistance is thought to be a factor in over five million deaths annually worldwide, posing a threat to public health and development. Antibiotic misuse and overuse are contributing to the global rise of AMR and negatively affecting the efficacy of these essential medications. The World Health Organization is striving to enhance the surveillance of antimicrobial resistance, decrease the overuse of antibiotics, and promote efficient antimicrobial stewardship programs through the Global Action Plan on AMR.[3-5] The WHO developed the AWaRe classification of antibiotics, which divides antibiotics into three groups: Access, Watch, and Reserve. These groups are based on the clinical importance of the antibiotics and the risk that

their use will promote resistance, emphasizing the need for appropriate use. This classification will aid in the development of tools for antibiotic stewardship at local, national, and global levels as well as reduce antimicrobial resistance.[6-8]

Normal flora and concentrations of bacteria (organisms per milliliter)[3]



List of Antibacterial Resistance Threats[4]

Urgent Threats

- Carbapenem-resistant Acinetobacter
- Candida auris (C. auris)
- Clostridioides difficile (C. difficile)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae (N. gonorrhoeae)

Serious Threats

- Drug-resistant Campylobacter
- Drug-resistant Candida
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant Enterococci (VRE)

■ Multidrug-resistant Pseudomonas aeruginosa (P. aeruginosa)

■ Drug-resistant nontyphoidal Salmonella

■ Drug-resistant Salmonella serotype Typhi

■ Drug-resistant Shigella

■ Methicillin-resistant Staphylococcus aureus (MRSA)

■ Drug-resistant Streptococcus pneumoniae (S. pneumoniae)

■ Drug-resistant Tuberculosis (TB)

Concerning Threats

Erythromycin-resistant group A streptococcus

Clindamycin-resistant group B streptococcus

Watch List

Azole-resistant Aspergillus fumigatus

Drug-resistant Bordetella pertussis

Drug-resistant Mycoplasma genitalium

Core Elements of Hospital Antibiotic Stewardship Programs[5,6]

WHO AWaRe classification of antibiotics

The WHO Expert Committee on Selection and Use of Essential Medicines designated antibiotics contained in the WHO Model Lists of Essential Medicines as Reserve, Watch, or Access in 2017, introducing the AWaRe classification for the first time.[7-9] The Expert Committee suggested in 2019 that the AWaRe categorization be extended to all regularly used antibiotics worldwide, outside of the WHO Model Lists. All antibiotics with widespread clinical applications worldwide are now categorized using the AWaRe framework, reflecting the recommendations of the Expert Committee on Selection and Use of Essential Medicines and guidance from the EML Antimicrobials Working Group. The WHO Expert Committee on Selection and Use of Essential Medicines' technical publications (WHO Technical Report Series) contain information on the methodology and supporting data for the recommendations.[9-11]

Policy makers, researchers, and healthcare professionals can utilize the AWaRe categorization as a tool to help with antibiotic prescribing, monitoring, and stewardship initiatives. The Access, Watch, Reserve (AWaRe) classification of antibiotics was created to aid in the creation of resources for antibiotic stewardship at the local, national, and international levels as well as to lessen antimicrobial resistance. Antibiotics are categorized into various groups to highlight the significance of their appropriate use.[10, 11] Countries are supposed to utilize this classification as a tool to help with antibiotic monitoring and stewardship initiatives. It is not meant to serve as a template for adding antibiotics to lists of critical medications for every country.

Access group antibiotics (A)

Compared to the antibiotics in the other categories, those in this group exhibit a lesser potential for resistance while still demonstrating effectiveness against a broad spectrum of frequently encountered susceptible infections. In order to improve access and encourage appropriate use, a number of antibiotics from the selected access group are listed as individual medications on the Model Lists of Essential Medicines. These medications are advised as essential first- or second-choice empirical treatment options for infectious syndromes reviewed by the EML Expert Committee.[11,12]

Amikacin	Amoxicillin/clavulanic-acid	Ampicillin/sulbactam
Amoxicillin	Ampicillin	Azidocillin

Bacampicillin	Mecillinam	Sulfaisodimidine
Benzathine-benzylpenicillin	Metampicillin	Sulfalene
Benzylpenicillin	Meticillin	Sulfamazone
Brodimoprim	Metronidazole_IV	Sulfamerazine
Cefacetrile	Metronidazole_oral	Sulfamerazine/trimethoprim
Cefadroxil	Nafcillin	Sulfamethizole
Cefalexin	Nifurtoinol	Sulfamethoxazole
Cefaloridine	Nitrofurantoin	Sulfamethoxazole/trimethoprim
Cefalotin	Ornidazole_IV	Sulfamethoxypyridazine
Cefapirin	Ornidazole_oral	Sulfametomidine
Cefatrizine	Oxacillin	Sulfametoxydiazine
Cefazedone	Penamecillin	Sulfametrole/trimethoprim
Cefazolin	Phenoxymethylpenicillin	Sulfamoxole
Cefradine	Pivampicillin	Sulfamoxole/trimethoprim
Cefroxadine	Pivmecillinam	Sulfanilamide
Ceftezole	Procaine-benzylpenicillin	Sulfaperin
Chloramphenicol	Propicillin	Sulfaphenazole
Clindamycin	Secnidazole	Sulfapyridine
Clometocillin	Spectinomycin	Sulfathiazole
Cloxacillin	Sulbactam	Sulfathiourea
Dicloxacillin	Sulfadiazine	Sultamicillin
Doxycycline	Sulfadiazine/tetroxoprim	Talampicillin
Epicillin	Sulfadiazine/trimethoprim	Tetracycline
Flucloxacillin	Sulfadimethoxine	Thiamphenicol
Furazidin	Sulfadimidine	Tinidazole_IV
Gentamicin	Sulfadimidine/trimethoprim	Tinidazole_oral
Hetacillin	Sulfafurazole	Trimethoprim

Watch group antibiotics (Wa)

This category comprises antibiotic classes with a greater potential for resistance, comprising the majority of the most important agents among the Critically Important Antimicrobials for Human Medicine1, as well as antibiotics that are at a comparatively high risk of bacterial resistance being selected against. These medications ought to be given top priority as important subjects for monitoring and stewardship initiatives. Selected antibiotics from the Watch group are listed as individual medications on the WHO Model Lists of Essential Medicines and are advised as first or second choice empiric therapy choices for a restricted number of particular infectious disorders.[10-12]

Arbekacin	Azithromycin	Bekanamycin	Carbenicillin
Aspoxicillin	Azlocillin	Biapenem	Carindacillin

Cefaclor
Cefamandole
Cefbuperazone
Cefcapene-pivoxil
Cefdinir
Cefditoren-pivoxil
Cefepime
Cefetamet-pivoxil
Cefixime
Cefmenoxime
Cefmetazole
Cefminox
Cefodizime
Cefonicid
Cefoperazone
Ceforanide
Cefoselis
Cefotaxime
Cefotetan
Cefotiam
Cefoxitin
Cefozopran
Cefpiramide
Cefpirome
Cefpodoxime-proxetil
Cefprozil
Cefsulodin
Ceftazidime
Cefteram-pivoxil
Ceftibuten
Ceftizoxime
Ceftriaxone
Cefuroxime
Chlortetracycline
Cinoxacin
Ciprofloxacin
Clarithromycin
Clofoctol
Clomocycline
Delafloxacin
Demeclocycline
Dibekacin
Dirithromycin
Doripenem
Enoxacin
Ertapenem
Erythromycin
Fidaxomicin
Fleroxacin
Flomoxef
Flumequine
Flurithromycin
Fosfomycin_oral
Fusidic-acid
Garenoxacin
Gatifloxacin
Gemifloxacin
Grepafloxacin
Imipenem/cilastatin
Isepamicin
Josamycin
Kanamycin_IV
Kanamycin_oral
Lascufloxacin
Latamoxef
Levofloxacin
Levonadifloxacin
Lincomycin
Lomefloxacin
Loracarbef
Lymecycline
Meropenem
Metacycline
Mezlocillin
Micronomicin
Midecamycin
Minocycline_oral
Miocamycin
Moxifloxacin
Nemonoxacin
Neomycin_IV
Neomycin_oral
Netilmicin
Norfloxacin
Ofloxacin
Oleandomycin
Oxolinic-acid
Oxytetracycline
Panipenem
Pazufloxacin
Pefloxacin
Penimepicycline
Pheneticillin
Pipemidic-acid
Piperacillin
Piperacillin/tazobactam
Piromidic-acid
Pristinamycin
Prulifloxacin
Ribostamycin
Rifabutin
Rifampicin

Reserve group antibiotics (Re)

Antibiotics and antibiotic classes included in this group should only be used to treat infections caused by multidrug-resistant organisms, whether they are proven or suspected. Antibiotics from the reserve group ought to be used as a "last resort." When an antibiotic from the Selected Reserve group has a favorable risk-benefit profile and demonstrated efficacy against "Critical Priority" or "High Priority" pathogens listed by the WHO Priority Pathogens List—particularly carbapenem-resistant Enterobacteriaceae—it is listed as an individual medication on the WHO Model Lists of Essential Medicines. These antibiotics ought to be available, but their application ought to be restricted to extremely particular people and situations, in whom all other options have either failed or are inappropriate. To maintain their efficacy, national and worldwide stewardship programs involving monitoring and utilization reporting could prioritize and protect these medications. [10-12]

Aztreonam
Ceftaroline fosamil
Ceftazidime-avibactam
Ceftobiprole medocaril
Ceftolozane-tazobactam
Colistin
Dalbavancin
Dalfopristin-quinupristin
Daptomycin
Eravacycline
Faropenem
Fosfomycin (IV)
Linezolid
Meropenem-vaborbactam
Minocycline (IV)
Omadacycline
Oritavancin
Plazomicin
Polymyxin B
Tedizolid
Telavancin
Tigecycline

Antibiotics not recommended

According to the worldwide standards, the use of the fixed-dose combinations of various broad-spectrum antibiotics described here is neither supported by evidence nor advised. The WHO advises against using them in therapeutic settings.[12]

acetylspiramycin/metronidazole
amikacin/cefepime
amoxicillin/bacillus coagulans/cloxacillin
amoxicillin/bacillus coagulans/dicloxacillin
amoxicillin/clavulanic acid/lactic ferments
amoxicillin/clavulanic acid/lactobacillus acidophilus
amoxicillin/clavulanic acid/nimesulide
amoxicillin/cloxacillin
amoxicillin/cloxacillin/lactic acid
amoxicillin/cloxacillin/lactobacillus acidophilus/serrapeptase
amoxicillin/cloxacillin/lactobacillus lactis
amoxicillin/cloxacillin/serrapeptase
amoxicillin/dicloxacillin
amoxicillin/dicloxacillin/saccharomyces boulardii
amoxicillin/flucloxacillin
amoxicillin/flucloxacillin/lactobacillus acidophilus
amoxicillin/metronidazole
amoxicillin/pivsulbactam
amoxicillin/sulbactam
ampicillin/bacillus coagulans/cloxacillin
ampicillin/cloxacillin

ampicillin/cloxacillin/lactobacillus acidophilus
ampicillin/cloxacillin/saccharomyces boulardii
ampicillin/dicloxacillin
ampicillin/dicloxacillin/lactobacillus acidophilus
ampicillin/flucloxacillin
ampicillin/lidocaine/sulbactam
ampicillin/oxacillin
ampicillin/sultamicillin
ascorbic acid/metamizole sodium/penicillin g /streptomycin
azithromycin/cefixime
azithromycin/cefixime/lactobacillus acidophilus
azithromycin/cefpodoxime proxetil
azithromycin/fluconazole/secnidazole
azithromycin/levofloxacin
azithromycin/ofloxacin
benzyl penicillin/streptomycin
bromelains/doxycycline/lactobacillus reuteri/lactobacillus rhamnosus/ornidazole
bromhexine/sulfamethoxazole/trimethoprim
cefaclor/clavulanic acid
cefadroxil/clavulanic acid

cefadroxil/trimethoprim
cefalexin/trimethoprim
cefdinir/clavulanic acid
cefepime/sulbactam
cefepime/tazobactam
cefixime/cefpodoxime proxetil
cefixime/clavulanic acid
cefixime/clavulanic acid/lactobacillus acidophilus
cefixime/cloxacillin
cefixime/cloxacillin/lactobacillus acidophilus
cefixime/dicloxacillin
cefixime/lactobacillus acidophilus/ofloxacin
cefixime/levofloxacin
cefixime/linezolid
cefixime/moxifloxacin
cefixime/ofloxacin
cefixime/ornidazole
cefoperazone/sulbactam
cefoperazone/tazobactam
cefotaxime/sulbactam
cefpodoxime proxetil/clavulanic acid
cefpodoxime proxetil/cloxacillin/lactobacillus acidophilus
cefpodoxime proxetil/dicloxacillin
cefpodoxime proxetil/dicloxacillin/lactobacillus acidophilus
cefpodoxime proxetil/levofloxacin
cefpodoxime proxetil/ofloxacin
cefpodoxime proxetil/sulbactam
ceftazidime/sulbactam
ceftazidime/tazobactam
ceftazidime/tobramicin
ceftibuten/clavulanic acid
ceftriaxone/sulbactam
ceftriaxone/tazobactam
ceftriaxone/vancomycin
cefuroxime axetil/clavulanic acid
cefuroxime axetil/linezolid
cefuroxime axetil/sulbactam
cefuroxime/clavulanic acid
cefuroxime/sulbactam
chloramphenicol/tetracycline

ciprofloxacin/metronidazole
ciprofloxacin/ornidazole
ciprofloxacin/tinidazole
doxycycline/tinidazole
erythromycin/sulfamethoxazole/trimethoprim
erythromycin/trimethoprim
fosfomycin/trimethoprim
gatifloxacin/ornidazole
kanamycin/penicillin g
levofloxacin/metronidazole
levofloxacin/ornidazole
meropenem/sodium/sulbactam
meropenem/sulbactam
metronidazole/norfloxacin
metronidazole/spiramycin
metronidazole/tetracycline
mezlocillin/sulbactam
ofloxacin/ornidazole
oleandomycin/tetracycline
piperacillin/sulbactam
rifampicin/trimethoprim
sulfadiazine/sulfamethoxazole/trimethoprim

Conclusion

Given the financial and staffing limitations, every hospital should make the most of its resources to assemble a cohesive team. The composition of the stewardship team need not be predetermined, and it would be a mistake to postpone implementing a stewardship program due to the unavailability of one or more of the members of the usual teams indicated below. A doctor who specializes in infectious disease, a pharmacologist who does not, or both, make up the majority of stewardship teams. This post is occasionally filled by a hospitalist who has an interest in infectious diseases. A successful program depends on close coordination with the administration, hospital epidemiology, and microbiology lab personnel. Getting involved with hospital leadership can help build positive relationships with other medical groups. Consequently, better acceptability and execution will result from the early involvement of thought leaders from hospital administration and the various practitioner groups.

One of the main objectives of the WHO's worldwide action plan to address antimicrobial resistance is to improve the quality of antibiotic use in hospitals. The WHO Essential Medicines List Access, Watch, and Reserve (AWaRe) classification may make it easier to implement straightforward stewardship measures that have broad worldwide applicability. In order to provide information for regional and national stewardship initiatives, we sought to publish statistics on trends of pediatric AWaRe antibiotic use.

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COVID-19 Status as of 24 December 2023

In the WHO South-East Asia Region, from 11 to 24 December 2023, 11 443 new COVID-19 cases and 74 deaths have been reported, a 235.4% and 311.1% increase compared to the previous 14 days, respectively. Between 11 and 24 December 2023, India (5 565 new cases, +331.1%), Indonesia (4 674, +426.9%), and Myanmar (36 new cases, +260.0%) reported an increase in the number of new cases, compared to previous 14 days. In the same period, Bangladesh reported 74 new cases which is similar to the number reported during the previous 14 days. Data were not available from Bhutan, Maldives, Nepal and Timor-Leste for this period.

General bed occupancy rates remain low in Delhi, India (0.10% as of 24 December 2023)2 and Indonesia (1.70% as of 24 December 2023); however, a small rise has been reported in the latter from 0.62% as of 1 December. The Region has recorded a cumulative total of 61 226 840 COVID-19 cases, including 808 166 deaths.

Globally, 772 838 745 COVID-19 cases, including 6 988 679 deaths have been cumulatively reported, as of 17 December 2023 4 .

Table 1. COVID-19 cases, deaths, and the weekly change in countries in the WHO South-East Asia Region in the week from 11 to 24 December 2023.

Country		Cumulative cases	New cases (last 14 days)	% change in new cases	New cases per 1M pop	Cumulative deaths	New deaths (last 14 days)	% change in new deaths	New deaths per 1M pop
India		45,008,620	5,565	331.1	4.0	533,333	27	237.5	0.0
Indonesia		6,819,830	4,674	426.9	17.1	161,954	31	1450.0	0.1
Thailand		4,761,781	1,069	-5.1	14.9	34,514	14	75.0	0.2
Bangaldesh		2,046,207	74	1.4	0.4	29,477	0	0.0	0.0
Sri Lanka		672,679	25	0.0	1.1	16,888	2	0.0	0.1
Myanmar		641,422	36	260.0	0.7	19,494	0	0.0	0.0
Bhutan		62,697	NA	NA	NA	21	NA	NA	NA
Maldives		186,694	NA	NA	NA	316	NA	NA	NA
Nepal		1,003,450	NA	NA	NA	12,031	NA	NA	NA
Timor - Teste		23,460	NA	NA	NA	138	NA	NA	NA
SEAR Total		61,226,840	11,443	235.4	NA	808,166	74	311.1	NA

*NA = data not available. DPR Korea has not reported confirmed COVID-19 cases. Thailand data were for the period from 10 to 23 December 2023 in comparison to the preceding 14 days. As for cumulative numbers, Maldives data are as of 5 August, Timor-Leste data as of 11 August, Bhutan data as of 8 October and Nepal data as of 20 October 2023.

SARS-CoV-2 variants of concern as of 5 January 2023

There are three variant categorization categories—variant under monitoring (VUM), variant of interest (VOI), and variant of concern (VOC)—to convey escalating levels of concern over a novel or developing SARS-CoV-2 variant.

Variants of Concern (VOC)

There are currently no SARS-CoV-2 variants meeting the VOC criteria.

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity
Omicron	BA.2.75 (x)	India	(y)	May 2022	Unclear	Similar to Baseline	No evidence
Omicron	XBB.1.5-like (a)	United States	N460K, S486P, F490S	n/a	Similar to Baseline	Reduced (v)	Similar to Baseline
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Unclear	Unclear	No evidence

Variants under monitoring

WHO label	Lineage + additional mutations	Country first detected	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity
Omicron	DV.7.1(link is external)	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence
Omicron	XBB.1.5(link is external)-like + L455F + F456L (b)	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence

Novel Drug Approvals for 2023

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
55.	Wainua	eplontersen	12/21/2023	To treat polyneuropathy of hereditary transthyretin-mediated amyloidosis
54.	Filsuvez	birch triterpenes	12/18/2023	To treat wounds associated with dystrophic and junctional epidermolysis bullosa
53.	Fabhalta	iptacopan	12/5/2023	To treat paroxysmal nocturnal hemoglobinuria
52.	Ogsiveo	nirogacestat	11/27/2023	To treat adults with progressing desmoid tumors who require systemic treatment
51.	Truqap	capivasertib	11/16/2023	To treat breast cancer that meets certain disease criteria
50.	Ryzneuta	efbemalenograstim alfa-vuxw	11/16/2023	To treat neutropenia
49.	Augtyro	repotrectinib	11/15/2023	To treat ROS1-positive non-small cell lung cancer
48.	Defencath	taurolidine, heparin	11/15/2023	To reduce the incidence of catheter-related bloodstream infections in adults with kidney failure receiving chronic hemodialysis through a central venous catheter
47.	Fruzaqla	fruquintinib	11/8/2023	To treat refractory, metastatic colorectal cancer
46.	Loqtorzi	toripalimab-tpzi	10/27/2023	To treat recurrent or metastatic nasopharyngeal carcinoma when used together with or following other therapies
45.	Omvoh	mirikizumab-mrkz	10/26/2023	To treat ulcerative colitis
44.	Agamree	vamorolone	10/26/2023	To treat Duchenne muscular dystrophy
43.	Bimzelx	bimekizumab	10/17/2023	To treat moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
42.	Zilbrysq	zilucoplan	10/17/2023	To treat generalized myasthenia gravis in adults who are anti-acetylcholine receptor (AChR) antibody positive
41.	Velsipity	etrasimod	10/12/2023	To treat moderately to severely active ulcerative colitis in adults

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
40.	Rivfloza	nedosiran	9/29/2023	To lower urinary oxalate levels in patients 9 years and older with primary hyperoxaluria type 1 and relatively preserved kidney function
39.	Pombiliti	cipaglucosidase alfa-atga	9/28/2023	To treat late-onset Pompe disease
38.	Exxua	gepirone	9/22/2023	To treat major depressive disorder
37.	Ojjaara	momelotinib	9/15/2023	To treat intermediate or high-risk myelofibrosis in adults with anemia
36.	Aphexda	motixafortide	9/8/2023	To use with filgrastim (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma
35.	Veopoz	pozelimab-bbfg	8/18/2023	To treat patients 1 year old and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease
34.	Sohonos	palovarotene	8/16/2023	To reduce the volume of new heterotopic ossification in adults and pediatric patients (aged 8 years and older for females and 10 years and older for males) with fibrodysplasia ossificans progressiva
33.	Elrexfio	elranatamab-bcmm	8/14/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy
32.	Talvey	talquetamab-tgvs	8/9/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior therapies
31.	Izervay	avacincaptad pegol	8/4/2023	To treat geographic atrophy secondary to age-related macular degeneration
30.	Zurzuvae	zuranolone	8/4/2023	To treat postpartum depression
29.	Xdemvy	lotilaner	7/25/2023	To treat Demodex blepharitis
28.	Vanflyta	quizartinib	7/20/2023	To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria
27.	Beyfortus	nirsevimab-alip	7/17/2023	To prevent respiratory syncytial virus (RSV)

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
				lower respiratory tract disease
26.	Ngenla	somatrogon-ghla	6/27/2023	To treat growth failure due to inadequate secretion of endogenous growth hormone
25.	Rystiggo	rozanolixizumab-noli	6/26/2023	To treat generalized myasthenia gravis in adults who are anti-acetylcholine receptor- or anti-muscle-specific tyrosine kinase antibody-positive
24.	Litfulo	ritlecitinib	6/23/2023	To treat severely patchy hair loss
23.	Columvi	glofitamab-gxbm	6/15/2023	To treat diffuse large B-cell lymphoma, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma after two or more lines of systemic therapy
22.	Inpefa	sotagliflozin	5/26/2023	To treat heart failure
21.	Posluma	flotufolastat F 18	5/25/2023	To use with positron emission tomography imaging in certain patients with prostate cancer
20.	Paxlovid	nirmatrelvir, ritonavir	5/25/2023	To treat mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19
19.	Xacduro	sulbactam, durlobactam	5/23/2023	To treat hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Acinetobacter baumannii-calcoaceticus complex*
18.	Epkinly	epcoritamab-bysp	5/19/2023	To treat relapsed or refractory diffuse large B-cell lymphoma (not otherwise specified) and high-grade B-cell lymphoma after two or more lines of systemic therapy
17.	Miebo	perfluorhexyloctane	5/18/2023	To treat signs and symptoms of dry eye disease
16.	Veozah	fezolinetant	5/12/2023	To treat moderate to severe hot flashes caused by menopause
15.	Elfabrio	pegunigalsidase alfa-iwxj	5/9/2023	To treat confirmed Fabry disease
14.	Qalsody	tofersen	4/25/2023	To treat amyotrophic lateral sclerosis in adults who have a SOD1 gene mutation
13.	Joenja	leniolisib	3/24/2023	To treat activated phosphoinositide 3-kinase

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
				delta syndrome
12.	Rezzayo	rezafungin	3/22/2023	To treat candidemia and invasive candidiasis
11.	Zynyz	retifanlimab-dlwr	3/22/2023	To treat metastatic or recurrent locally advanced Merkel cell carcinoma
10.	Daybue	trofinetide	3/10/2023	To treat Rett syndrome
9.	Zavzpret	zavegepant	3/9/2023	To treat migraine
8.	Skyclarys	omaveloxolone	2/28/2023	To treat Friedrich's ataxia
7.	Filspari	sparsentan	2/17/2023	To reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression
6.	Lamzede	velmanase alfa-tycv	2/16/2023	To treat non-central nervous system manifestations of alpha-mannosidosis
5.	Jesduvroq	daprodustat	2/1/2023	To treat anemia caused by chronic kidney disease for adults on dialysis for at least four months
4.	Orserdu	elacestrant	1/27/2023	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy
3.	Jaypirca	pirtobrutinib	1/27/2023	To treat relapsed or refractory mantle cell lymphoma in adults who have had at least two lines of systemic therapy, including a BTK inhibitor
2.	Brenzavvy	bexagliflozin	1/20/2023	To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise
1.	Leqembi	lecanemab-irmb	1/6/2023	To treat Alzheimer's disease

Disclaimer: This bulletin aims to arm healthcare professionals with up-to-date, trustworthy information about medications and other relevant topics so they may make educated decisions when recommending medications to patients. Due to the lack of comprehensive data on novel treatments or interventions, it is justified to continuously update with this information whenever it becomes available. No one connected with the bulletin's publishing, nor the organization, shall bear any liability for any harm brought about by using the contents of this publication. If medication brand names are provided, they are solely included for illustration purposes; the bulletin does not recommend them.

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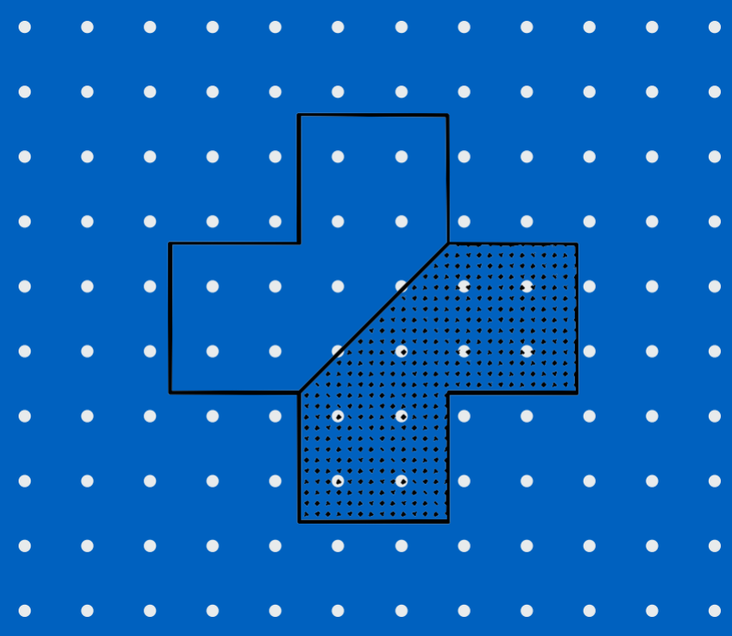

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