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The International Congress of Pathology & Laboratory Medicine 2023: Precision Medicine: Revolutionizing Pathology in Genomic Era, organised by the College of Pathologists, Academy of Medicine of Malaysia and at World Trade Centre Kuala Lumpur on 20-22 September 2023

ICPALM 2023: International speakers

1. Anatomical Pathology

Molecular classification of gastric carcinoma
Corrado DÁrrigo
Poundbury Cancer Institute.

During the past two decades there has been significant improvement of cancer outcomes due, at least in part, to increasing use of biological therapies. This requires the identification of specific subgroup of patients that may benefit from particular targeted treatment. The classical morphological classification of tumours is inadequate to support this transformation of treatment modalities. New molecular classifications have emerged for a number of cancer sites, based on comprehensive analyses of large number of parameters ("multi-omics"). In order to make it accessible to all patients, multi-omics classifications have been implemented into the histopathology diagnostic routine using a handful of on-slide tests.

Such implementation has yet to happen in gastric cancer (GC) and patients access to effective targeted treatment remains limited. We present an overview of the current molecular classification for gastric cancer and a study to assesses the feasibility of implementing a molecular classification based on 4 groups of on-slide tests. These are ISH for EBER (for the identification of GC EBV+), IHC for MLH1 and MSH2 (for the identification of GC MMR-deficient), IHC for E-cadhering and β-catenin (for the identification of GC EMT or epithelial-mesenchymal transformation) and IHC for p53 (for the identification of p53 mutated and p53 wild type GC). The prognostic and predictive implications for GC patients will be discussed.

Rewriting the Her2 testing handbook
Corrado DÁrrigo
Poundbury Cancer Institute.

Histopathologists have been providing Her-2 status for breast cancer (BC) patients for over 4 decades. Testing aimed at identifying a small (12-15%) proportion of BC patients that have Her2 gene amplification as a main oncogenic driver in their cancer. Direct blocking of the Her2 receptor with mAb-based therapy is an effective treatment only in patients with Her2 over-expression or amplification.

Recently, targeting Her2 with specific antibodies that deliver cytotoxic payloads inside the tumour cells (ADC or antibody-drug conjugates) has shown effectiveness also in BC that has low level expression of Her2 but lacks amplification. Regulatory approval of this treatment means de facto that the traditional binary classification (positive/negative) has to be replaced with a new ternary classification (high/low/zero) and that the interpretation of the IHC staining needs to be re-focused to recognise the new thresholds.

We developed focused algorithms and training programmes for the interpretation of Her2 IHC in the new diagnostic landscape. We will be discussing the re-evaluation of the scope and parameters for Her2 testing in BC with particular focus on the analytical performance of current tests, the identification of various staining patterns and their significance, the interpretative algorithm and the new (2023) release of the ASCO-CAP and RCPath guidelines.

Surgical pathology of low-grade epilepsy-associated neuroepithelial tumors (LEAT): role of molecular genetic testing and surrogate immunohistochemical markers
Hajime Miyata
Departments of Neuropathology, Research Institute for Brain and Blood Vessels, Akita Cerebrospinal and Cardiovascular Center in Akita City, Japan

Low-grade epilepsy-associated neuroepithelial tumors (LEAT) is a generic term for CNS WHO grade 1 to 2 or equivalent tumors, with epileptic seizures as the main symptom developing mostly by the age of 15 years, and 88% of patients show a favorable postoperative seizure outcome, representing a clinicopathological concept distinct from the WHO classification of brain tumors. A past survey reported that the majority of LEAT consisted histopathologically of neuronal and mixed neuronal-glial tumors frequently localized in the temporal lobe, with ganglioglioma (GG) and dysembryoplastic neuroepithelial tumor (DNT) being the most common histopathological diagnoses comprising 60 to 90 % of cases. However, disagreement between experts on diagnosing GG and DNT was not uncommon, particularly when specific histological features were not

observed. Some LEAT may be difficult to diagnose following the current WHO classification, and others may need to be differentiated from non-neoplastic lesions. Tumor cells in LEAT are characterized immunohistochemically by negative or weak MAP2 expression with a low Ki-67 labeling. CD34 expression in neoplastic and other neuroepithelial "ramified" cells is suggestive of LEAT with MAPK pathway alteration, such as *BRAF* and *FGFR* alterations, constituting the major genetic pathogenesis of LEAT. BRAF V600E-mutant protein is the only surrogate immunohistochemical marker for a specific genetic alteration in this pathway. Genetic and epigenetic analyses in LEAT are important to rule out astrocytoma-oligodendroglioma-glioblastoma lineage and may contribute to the final integrated diagnosis. Randomized controlled trials would be warranted to clarify clinicopathological correlation, including postoperative seizure outcomes and the development of any specific molecularly-targeted therapies.

Surgical pathology of intracranial vascular malformations and molecular genetic background

Hajime Miyata
Departments of Neuropathology, Research Institute for Brain and Blood Vessels, Akita Cerebrospinal and Cardiovascular Center in Akita City, Japan

Brain arteriovenous malformation (b-AVM) and cerebral cavernous malformation (CCM) are the most frequent among intracranial vascular malformations (VMs) encountered in surgical pathology. Microscopically, b-AVM consists of abnormally dilated, malformed, thick and thin-walled, hyalinized vessels, apparently neither artery nor vein, with intervening brain parenchyma. CCM consists of thin-walled, irregularly dilated venous vessels arranged in a back-to-back pattern without intervening brain parenchyma. Historically, these VMs were considered a group of presumably congenital blood vessel abnormalities resulting from disordered mesodermal differentiation in the developing human embryo between the 3rd and 8th weeks of gestation. However, they are, in fact, dynamic rather than static lesions showing *de novo* formation, progressive growth and repetitive hemorrhages, spontaneous regression, and recurrence after complete resection, supporting the postnatal growth of these VMs. Recent genetic studies revealed molecular genetic backgrounds of sporadic VMs distinct from relatively rare familial/hereditary counterparts. Somatic mutations in the RAS-MAPK signaling pathway, particularly *KRAS* (62.5 to 76.2%), may play a significant role in genetic susceptibility/predisposition in the pathogenesis of sporadic b-AVMs. Hereditary AVMs in Osler-Weber-Rendu disease and capillary malformation-AVM are associated with defects in the TGF-β/SMAD signaling (*endoglin*, *ACVRL1*/*ALK1*, *SMAD4*) and RAS-MAPK signaling pathway activation (*RASA1*), respectively. On the other hand, somatic activating mutations in the PI3K-AKT-mTOR signaling pathway, particularly *PIK3CA* (39%), are detected in sporadic single CCMs, and pericyte is the probable cell of origin. Familial multiple CCMs are associated with germline mutations in a heterotrimeric CCM complex (*CCM1*/*KRIT1*, *CCM2*/*MGC4607*, *CCM3*/*PDCD10*), affecting the junctional integrity between neighboring vascular endothelial cells in familial multiple CCMs.

Innovative technologies in precision oncology

Zisis Kozlakidis
Laboratory Services and Biobanking at the World Health Organisation International Agency for Research on Cancer

Healthcare is undergoing a transformation, utilising novel technologies to generate new data and support the advent of precision medicine. The scientific breakthroughs and technological advancements of the last two decades have improved our understanding of disease pathogenesis and changed the way that many cancers are diagnosed and treated, leading to more precise, predictable and powerful healthcare that can be potentially customised for the individual patient. The deep genomic profiling, for example utilising next-generation sequencing technologies (NGS) for large panels, in combination with the detailed clinical information, can result in a comprehensive understanding of the genomic drivers of a number of cancers, such as lung cancer. This presentation will focus on the opportunities that these technologies offer in the understanding and, eventually, treatment of cancer.

2. Chemical Pathology

Next-Generation Sequencing for Cardiometabolic Disorders

Amanda Jane Hooper
Department of Clinical Biochemistry, PathWest Laboratory Medicine WA, Fiona Stanley Hospital Network, in Perth, Western Australia

The Cardiovascular Genetics Laboratory (PathWest, Perth, Australia), has provided a diagnostic genetic testing service for inherited cardiometabolic disorders for over 15 years. The laboratory primarily services cardiometabolic clinics at major tertiary hospitals in Western Australia, but also receives samples referred from interstate and international centres, particularly for rare lipid disorders. Next-generation sequencing has enabled the expansion of testing to diagnose a range of inherited cardiometabolic disorders including familial hypercholesterolaemia and hypertriglyceridaemia, monogenic diabetes, inherited lipodystrophies and primary aldosteronism. A genetic diagnosis may assist with patient management, and can facilitate screening of family members for these mostly dominantly-inherited disorders.

Inherited Lipid Disorders
Amanda Jane Hooper
Department of Clinical Biochemistry, PathWest Laboratory Medicine WA, Fiona Stanley Hospital Network, in Perth, Western Australia

Inherited lipid disorders affect the levels of cholesterol and/or triglyceride in the circulation and, if untreated, can lead to severe multisystem complications. This presentation aims to provide an overview of selected genetic lipid disorders, focusing on the recommended diagnostic strategies. Familial hypercholesterolaemia is the most common monogenic lipid disorder, affecting 1 in 250 individuals worldwide, causing elevated LDL-cholesterol leading to premature atherosclerosis if untreated. Rarer inherited lipid disorders include the familial chylomicronaemia syndrome, and disorders causing low HDL- and LDL- cholesterol (hypoalphalipoproteinaemia and hypobetalipoproteinaemia). Studying naturally-occurring mutations in lipid disorders provides insight into the mechanisms underlying lipoprotein production and metabolism and has enabled the development of treatments for dyslipidaemias.

Chylomicronaemia
Amanda Jane Hooper
Department of Clinical Biochemistry, PathWest Laboratory Medicine WA, Fiona Stanley Hospital Network, in Perth, Western Australia

Chylomicronaemia is characterised by the persistence of chylomicrons in the circulation. Plasma triglycerides >10 mmol/L in the fasting state indicates the presence of chylomicrons. Familial chylomicronaemia syndrome (FCS) encompasses a group of recessive gene defects, usually caused by pathogenic variants in the lipoprotein lipase (LPL) gene, leading to very high triglyceride levels and eruptive xanthomata, hepatosplenomegaly and recurrent episodes of acute pancreatitis. FCS is extremely rare, affecting roughly 1 in 500,000. More commonly, chylomicronaemia syndrome is multifactorial or polygenic in nature, with risk of hypertriglyceridaemia influenced by factors including obesity, diabetes and alcohol. Rarely, auto-antibodies to proteins involved in the LPL lipolytic pathway can cause chylomicronaemia.

The investigation of inherited and acquired metabolic disease - what tests will provide answers?
Simon Olpin
Sheffield Children's Hospital, NHS Foundation Trust, Sheffield, UK.

This presentation assumes a significant existing understanding of metabolic disease. The talk first gives a brief introduction to inherited and acquired metabolic disease followed by the recognition of the importance of the type of clinical presentation which may give vital clues to pursue towards a diagnosis. It is always important to undertake basic biochemical investigations that may provide possible pointers to pursue through specific metabolic testing. For many metabolic disorders important diagnostic pointers or indeed very strong diagnostic information may follow through three relatively easily accessible metabolic tests. These tests are generally available in specialist metabolic laboratories namely urine organic acids, blood acylcarnitines and blood and urine amino acids. Other specialised metabolic tests may need to be undertaken if these former tests do not provide clear pointers to diagnosis. Three clinical cases are then presented to illustrate important points. The three cases include a case of hypoglycaemia in a one-year-old infant, metabolic acidosis in a 54-year-old woman and sudden onset muscle weakness, reduced consciousness and unexplained encephalopathy in a previously well 17-year-old female. Looking to the future, advances primarily in MS/MS technology will give much improved sensitivity with the ability to detect a greatly expanded range of metabolites and this will form second generation metabolomics. Second generation metabolomics will include lipidomics which will open up additional important diagnostic lipid profiles. Second generation metabolomics run in conjunction with WGS/WES will allow more specific pairing of metabolic profiles to specific genes with great advances in diagnosis. Overall conclusions are then clearly set out.

3. Forensic Medicine

ICRC and Humanitarian Forensic Action
Davette Gadison
International Committee of the Red Cross (ICRC), Bangkok

This presentation will introduce a brief history of the development of humanitarian forensic action and the Forensic Unit within the International Committee of the Red Cross. Topics such as relevant international laws, such as International Humanitarian Law, Human Rights Law, and Customary Law, that provide protection for the deceased and obligations of states will be introduced. In addition, the presentation will touch upon how the International Committee of the Red Cross promotes the aforementioned laws through the work of the Forensic Unit and how the institution supports states, local institutions, communities etc. regarding protection of the deceased and their families.

Sudden Cardiac Death and Molecular Autopsy
Mary Sheppard
St George's, University of London

Sudden cardiac death (SCD) is an important public health problem worldwide, accounting for an estimated 6 to 20% of total mortality. A significant proportion of SCD is caused by inherited heart disease, especially among the young. An autopsy is necessary to establish a diagnosis of inherited heart disease allowing for subsequent identification of family members that require cardiac follow-up. Autopsy of cases of unexplained sudden death in the young is recommended by both the European Society of Cardiology and the American Heart Association, albeit with different age cutoffs. Overall autopsy rates, have been declining in many countries across the globe and recent studies show that not all cases of sudden death in the young are autopsied, likely due to monetary and organizational limitations and lack of awareness among police, legal authorities, and physicians. Autopsy rates further decline with increasing age in persons below the age of 50 years. Consequently, diagnoses of inherited heart disease are likely missed, along with the opportunity for treatment and prevention among surviving relatives. Sudden cardiac death (SCD) is a major public health problem worldwide and an important cause of both cardiovascular and total mortality. A significant proportion of SCD occur in persons of working age, and SCD consequently constitutes a significant societal burden in addition to the immense personal consequences of these events. My lectures will deal with the diagnosis of the leading causes of SCD which is Ischaemic heart disease, sudden adult death and cardiomyopathies. Overall, detailed cardiac and genetic investigations of first-degree relatives of SADS cases or SCD on basis of potentially inherited structural heart disease results in a diagnosis of inherited cardiac disease in around 20-50% of the families.

SIDS - Current Issues of Concern
Roger Byard
Department of Pathology, University of Adelaide, South Australia, Australia

Recent studies in South Australia have shown that there has been a 12% fall in the number of published peer-reviewed papers on SIDS listed on Pubmed that correctly cite standard definitions. Almost two thirds of studies between 2019-2021 had no, or non-standard, definitions. Although infant death rates in South Australia between 1994-98 and 2014-18 have shown a marked decline in SIDS cases (55 to 12), this has been accompanied by a corresponding increase in the numbers of cases classified as "undetermined" (5 to 18). When the two groups are merged (60/80vs30/56) no significant changes have occurred ($p=0.26$). Failure to use standard definitions and changing diagnostic terminology may, therefore, have markedly influenced recent apparent changes in infant mortality. Research papers are also being published where cases have been classified as SIDS without even an autopsy being performed. In view of these developments how can we correctly interpret conclusions relating to SIDS research if studied cases do not fulfil standard criteria, and how can we accurately monitor trends in SIDS mortality if there is diagnostic shift?

SIDS - Possible Aetiological Mechanisms
Roger Byard
Department of Pathology, University of Adelaide, South Australia, Australia

There have been major developments in recent years in the understanding of pathophysiological mechanisms for SIDS involving predominantly neuropathological and neurotransmitter abnormalities. Research into serotonin and substance P deficiencies will be described. It is also now clear that there are both epidemiological and neuropathological differences between infants who die alone (classical SIDS) and those who die in shared sleeping situations (co-sleeping). Deficiencies in brainstem substance P could explain vulnerabilities of certain infants to the prone position.

Non-Accidental Injuries - Overview and Pitfalls
Roger Byard
Department of Pathology, University of Adelaide, South Australia, Australia

There are many factors to consider when trying to distinguish accidental from non-accidental injury in infants and children. Clinical findings and radiologic imaging studies not in keeping with the history, and injuries of different ages, are key indicators of inflicted trauma, especially in the very young. An independent witness to the traumatic event may be important for corroborating or negating a carer's version of the history. The age and stage of development of the child (e.g. could he/she move enough to become injured?), the timeliness of seeking treatment, other injuries (especially injuries of different ages), and the child's state of nutrition and cleanliness should all be taken into consideration when separating inflicted from non-inflicted injuries. Abusive injuries tend to occur at odd hours, are allegedly unwitnessed by carers, and are often attributed to the actions of siblings. Issues with the dating of bruises, the assessment of carer's histories and inflicted head trauma will be focused on.

4. Genetic Pathology

Future developments in genomic medicine
David Amor
Murdoch Children's Research Institute

2023 marks the 20th anniversary of the completion of the human genome project. Whilst translation of genomics into health care was initially slow, this is now accelerating, and it is estimated that by the 40th anniversary, most people in developed countries will have had their genome sequenced. In this talk I will discuss recent successes in genomics, including the identification of causes of intellectual disability and rapid diagnosis of critically ill infants. As the cost of sequencing falls, we expect to see increased use of genome sequencing in healthy individuals, including for newborn screening, with the aim of diagnosing rare diseases early and using genomic information to predict and prevent common diseases. The ultimate goal will be the integration of genomic data and clinical data within the electronic medical record, with aggregated datasets promising new insights into disease risk and mechanisms. In reproductive medicine we expect to see increased use of preconception carrier screening, along with use of genomic sequencing on prenatal diagnosis samples. In the next 20 years, genomics will herald a new era of precision medicine, but its success will require extensive education of doctors, scientists and the general public, as well as addressing bioethical and psychosocial aspects.

Genetics of neurodevelopmental disorders
David Amor
Murdoch Children's Research Institute

The search for causation is a key component of the assessment of child with neurodevelopmental disorders. Historically, a specific diagnosis was achievable in only a minority of these children, but over the last decade, this has changed dramatically such that a specific diagnosis is possible in about half of all children with intellectual disability, with more recent studies demonstrating diagnostic yield in cerebral palsy, autism and speech disorders. This improvement has been driven by advances in genetic-testing technologies, most importantly chromosome microarray and whole exome sequencing. Simultaneously, these technological advances have revealed many new genetic syndromes that had previously escaped clinical recognition and demonstrated that most severe intellectual disability is caused by pathogenic gene variants that arise de novo in the child. Evidence from health economic studies suggests that this testing is most cost effective when performed early in the patient's diagnostic journey. The next challenges are to harness new research technologies to diagnose previously unsolved cases, and to understand how the combination of rare and common gene variants combine to cause the final phenotype.

Ethical issues in prenatal screening using NIPT: A multifaceted perspective
Mark Pertile
Divisions of Reproductive Genetics and Biochemical Genetics at the Victorian Clinical Genetics Services in Melbourne, Australia

Non-Invasive Prenatal Testing (NIPT) represents a significant advance in prenatal care. Some versions incorporate a more comprehensive assessment of fetal genetics, including screening for sex chromosome conditions, rare autosomal trisomies, and segmental chromosome conditions. While such screening can provide valuable insights into fetal health, it also presents a complex set of ethical challenges. This presentation explores ethical issues associated with NIPT from the perspectives of doctors, patients, and laboratory providers, and sheds light on some of the complexities emerging from the use of this rapidly expanding technology.

Exploring the origins of false NIPT results using single nucleotide polymorphism (SNP) microarray
Mark Pertile
Divisions of Reproductive Genetics and Biochemical Genetics at the Victorian Clinical Genetics Services in Melbourne, Australia

While Non-Invasive Prenatal Testing (NIPT) is known to be highly accurate, false-positive and false-negative results occur at low frequency. This may be due to placental and/or fetal mosaicism, which can remain undetected in the absence of appropriate genetic investigations. Single nucleotide polymorphism (SNP) microarray on DNA from placental and fetal tissues enables a thorough investigation of the genetic constitution of this cellular material. The SNP genotyping data generated by microarray can also provide insights into the origins of aneuploidy and structural chromosomal rearrangements, thereby exposing possible causes of false results obtained using NIPT. Examples from our clinical laboratory services are used to highlight the benefits of these investigations.

5. Microbiology

Important role that genomics play in diagnosing and managing emerging and re-emerging viral infections
Vincent TK Chow
Host And Pathogen Interactivity Laboratory, Yong Loo Lin School of Medicine, National University of Singapore

The COVID-19 pandemic offers excellent opportunities to capitalize on and further adopt genomics and related strategies (including epigenetics, transcriptomics, proteomics, metabolomics and other omics) to improve the diagnosis, prognosis, management, treatment and surveillance of emerging and re-emerging viral and other infectious diseases. Advances in next generation sequencing enable detailed characterization of SARS-CoV-2 variants, sub-variants and quasispecies of varying virulence, ranging from Alpha to Omicron. Public databases such as GISAID facilitate the rapid dissemination and worldwide sharing of viral genome sequences. Such applications contribute immensely to early identification and monitoring of new outbreaks which lead to prompt and appropriate public health interventions for infection control. Other direct applications that rely critically on viral genomic data include the design of mRNA and recombinant vaccines, and the detection of antiviral resistance mutations. Genome-wide association studies (GWAS) and other genetic analyses can identify polymorphisms or variants of genes associated with severe COVID-19 – examples include ACE2, TMPRSS2, TMPRSS11A, apolipoprotein E, cathepsin L, certain HLA alleles, toll-like receptor 3, TLR7, neutrophil elastase, mannose-binding lectin 2, MAVS, IFNAR2, IFITM3, interleukin-6, CXCR6, CCR5 and CCR9 chemokine receptors. Polymorphisms in drug-metabolizing genes are also clinically relevant, e.g. functional variants of cytochrome P450 CYP2D6 which is involved in remdesivir metabolism may influence the pharmacodynamics of this antiviral agent. The efficacy and adverse effects of COVID-19 vaccines are also associated with certain immune regulatory gene polymorphisms. In addition to clinical studies, animal models also contribute significantly in identifying and evaluating novel host response biomarkers which aid in prediction of disease severity and triaging of patients. Examples of useful biomarkers of COVID-19 severity include C-reactive protein, procalcitonin, lactate dehydrogenase, interleukin-6 (and other pro-inflammatory cytokines), and angiopoietin-like 4. Metagenomics is also exploited for animal and environmental surveillance, as well as wastewater monitoring of relevant viral pathogens. Genomics and other omics technologies will play increasingly important roles in precision medicine, precision public health and planetary health in the management and research of emerging and re-emerging viral diseases.

Persistent TST and IGRA non-conversion to *Mtb* exposure in persons living with HIV in Cape Town, South Africa
Elouise Kroon
Stellenbosch University, South Africa

Tuberculosis (TB) remains one of the leading causes of death due to communicable disease worldwide. Persons living with HIV (PLHIV) are especially affected and are more likely to develop TB than HIV negative persons. Despite this, there are PLHIV who live in high TB incidence environments like the Western Cape and never become infected with *Mycobacterium tuberculosis* (*Mtb*) as inferred from a negative tuberculin skin test (TST) and interferon gamma release assay (IGRA). In addition, this group does not have current or previous TB. We identified 48 of these persons aged 35-60 years old and defined this group as HITTIN. HITTIN displayed *Mtb*-specific antibody responses, confirming prior *Mtb* exposure. At the same time we enrolled 35 PLHIV, with no TB history, but who tested persistently TST and IGRA positive (HIT) and 39 PLHIV with a history of previous TB, all between the ages of 35-60 years old. Whole genome sequencing and single-cell RNA sequencing analysis from bronchoalveolar lavage samples are underway. In a substudy we investigated the difference in gene expression in response to *Mtb* infection between neutrophils from HITTIN (PMN_{HITTIN}) and neutrophils from HIT (PMN_{HIT}). PMN_{HITTIN} displayed a globally lower differential gene expression response to *Mtb* infection after 6h compared to PMN_{HIT}. Further research is required to understand the role of neutrophils in this resister phenotype and elucidating the possible complex relationship between neutrophils and non-interferon gamma T-cell responses.

The Pros and Cons of Molecular Diagnosis in Parasitic Infections
Harshvardhan Sheorey
Microbiology Department, St Vincent's Hospital, Melbourne, Australia, and Microbiology Department, Royal Melbourne Hospital, Australia.

Parasitology is the neglected section of microbiology, especially in developed countries. Molecular diagnosis has become routine and advanced for virology and most of bacteriology and advances in mycology are progressing. Although there are good testing algorithms for Protozoa, we have just started seeing some advances in helminth, but almost nothing for arthropods. The advantages and disadvantages of what is available at this time will be discussed.

Clinical case-based presentation in Parasitology (use of e-diagnosis)
Harshvardhan Sheorey
Microbiology Department, St Vincent's Hospital, Melbourne, Australia, and Microbiology Department, Royal Melbourne Hospital, Australia.

Difficult-to-diagnose interesting cases in parasitology will be discussed. The use of an international team of experts (e-diagnosis team) will be introduced and examples of how this team helps will be presented.

Sick Building Syndrome
Malcolm Richardson
Mycology Reference Centre, Manchester University, NHS Foundation Trust, United Kingdom

People spend a substantial fraction of their lives indoors (often 80-90%) and so these locations can represent a significant fraction of exposure to air pollution. Indoor air quality is a complex phenomenon but has been studied far less than air quality outdoors. In the absence of indoor sources of pollution, indoor air quality is determined by ingress of outdoor air, balanced with pollutant loss processes such as deposition to surfaces and through ventilation. Moulds are responsible for diseases in humans through the three pathogenetic mechanisms of infection, allergy, and toxicity. Fungal infection is especially a risk factor for immunodeficient patients, but it occurs in immunocompetent patients as well. Climate change adaptation and mitigation policies and net zero technologies may lead to a range of impacts that could alter airtightness, temperature and humidity indoors, which in turn may lead to changed behaviours around ventilation and building management, all contributing to the concept of a 'sick building'. Indirect climate change effects such as increases in humidity, may degrade indoor air quality as a consequence of increased prevalence of moulds and damp, in turn increasing concentrations of fungal conidia. Changes in lifestyle and working patterns may also impact on indoor air quality (and more broadly the spread of moulds), for example increasing time spent at home, or in shared co-working environments. It is critical that the possible impacts of future technological or behavioural changes on indoor air quality are evaluated routinely in policymaking and cross-government mechanisms developed further to consider these effects.

ICPALM 2023: Local speakers

1. Anatomical Pathology

Challenging cases in female genital tract (Chapter: Ovary)
Angeline Binti Madatang
Department of Pathology, Queen Elizabeth Hospital

Ovarian cancer is the 8 th most common cancer diagnosis and cause of cancer death in women. Among the histological type, sex cord-stromal tumour and metastases to the ovary present uniqueand particular challenges to arrive at an accurate diagnosis especially in a centre with limited resources. In ovarian sex-cord stromal tumour classic forms, these heterogenous group of uncommon neoplasm are relatively easy to diagnose. The challenge is the considerable overlap in morphological features between various other tumour types. Immunohistochemistry, although is useful to confirm sex cord-stromal tumour has little value to separates the types accurately. Recent findings of somatic FOXL2 mutation in >90% of adult granulosa cell tumour, DICER1 mutation (somatic or germline) in a proportion of moderately and poorly differentiated Sertoli-Leydig cell tumour and microcystic stromal tumour contain CTNNB1 or less frequently APC mutation and may occasionally be an extracolonic manifestation of FAP are very recent significant advances. In the other hand, ovary is also the common site of metastasis within the gynaecological tract. Metastases in the ovaries can present synchronously or metachronously with the primary neoplasm and sometimes represent the first manifestation of disease and mimic primary ovarian tumour and causing error in diagnosis.

Biobanking in medical research: Our experiences in setting and managing the UMBI-HCTM Biobank
Nor Azian Abd Murad
Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia.

Biobanking is essential in medical research as it stores biological samples in an organised biorepository and it contains information on the patients. Biobanking aims to archive patient samples with demographic and clinical data that could enhance discovery research as well as the development of precision and personalized medicine and future medical research. The appropriate definition of the biobank is a vast collection of biospecimens connected to the participant's personal and health information, such as environmental factors including lifestyle and dietary intake, personal and family history of diseases and genetic information for the use of health and medical research. ISO 20387:2018 defines a biobank as a legal party that performs activities related to sample collection, preparation, preservation, testing, analysis and distribution of biological samples and the relevant data. The UMBI-HCTM Biobank was established in 2004 for future research purposes and the protocols and consent form were approved by the Research Ethics Committee of UKM (RECUKM). Samples collected from the Hospital Canselor Tuanku Muhriz (HCTM) include non-cancer and cancer cases. For non-cancer, blood samples were collected; cancerous tissue samples were collected with the adjacent normal tumour and the blood samples for cancer cases. Blood samples were processed for serum, plasma mononuclear *cells* and DNA. In total, 4629 samples for non-cancer cases and 4383 for cancer cases have been collected. This sharing session will discuss all critical aspects of biobanking, including governance, ethical issues, financial and personnel resources, samples and data security. In addition, the need for adequate information technology that includes extensive computing hardware and software in biobanking will also be discussed.

Biobanking initiatives in Ministry of Health Malaysia
Hans Prakash Sathasivam
Institute for Medical Research, Malaysia.

Biobanking activities for future research have been carried out for many decades in the Ministry of Health, with most of these activities being project-based and linked to specific research groups. The Ministry of Health (MOH) Biobank was established to consolidate and optimize resources for sustainable biomedical research as well as to streamline biobanking activities in MOH. The MOH Biobank has been involved with the collection of various types of tissue & associated anonymised data from donors who have given their informed consent for future research. The MOH Biobank is currently in the midst of establishing a biobanking network within MOH to enhance the collection, processing, storage and distribution of quality biospecimens. The main aim of the MOH Biobank is to facilitate and accelerate biomedical research in Malaysia by providing high-quality biospecimens and associated data.

Molecular revolution: What's next in epilepsy?
Nor Haizura Abd Rani
Department of Pathology, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, formerly at General Hospital Kuala Lumpur, Malaysia.

A "long-term epilepsy-associated tumours (LEATs)" was introduced to recognize rare tumour entities in patients with drug-resistant long-term epilepsy that do not match with the WHO description and nosology, but are likely closer to the disease spectrum. It is the second most common after hippocampal sclerosis. The histopathological classification of LEAT remained ever-challenging due to variable microscopic features including cellular components difficult to differentiate from preexisting neurons, and multiple architectural growth patterns occurring in many LEAT entities. However, inter- and intra-rater agreement is poor for the differential diagnosis of LEAT, also affecting the WHO grading. Molecular neuropathology has revolutionized our understanding of tumour classification strategies and their impact on clinical treatment. However, these studies have very much focused on malignant tumours rather than LEAT. In addition, commonly described molecular genetic findings do not play a role in LEAT, such as IDH1R132H, 1p/19q co-deletions, TERT promotor mutations or MGMT DNA methylation. Hence, BRAF V600E, FGFR1, FGFR2, MYB/ L1 and PRKCA gene alterations have been recognized in common LEAT entities and likely translate into specific subgroups. DNA methylation array analysis has supported this notion but needs further corroboration, in particular by addressing large enough and prospectively collected patient cohorts with LEAT.

HER2 testing in oesophageal and gastric adenocarcinoma in Malaysia. An early days analysis
Pavitratha Puspanathan
Department of Pathology, Hospital Pulau Pinang, Malaysia.

In recent years, it has become increasingly apparent that HER-2 testing in advanced gastroesophageal adenocarcinomas plays an important role for therapeutic decisions. HER-2 testing, both immunohistochemistry and in-situ hybridization has become common place testing for breast carcinoma in Malaysia with at least immunohistochemistry being widely available in most histopathology laboratories. However, HER-2 testing for gastroesophageal adenocarcinomas is not yet widely performed. This presentation looks at our early experience with HER-2 testing in gastroesophageal adenocarcinomas as well as relevant clinicopathological information.

Molecular Profiling for Precision Cancer Therapies
Sayyidi Hamzi
Reference Specialised Laboratory, and a Research, Development and Innovation Manager at Premier Integrated Labs Sdn Bhd.

Understanding of the molecular mechanisms in cancer have evolved rapidly over recent years, and the different condition from one patient to another is now widely recognised. There are no terms as one-size-fits-all approaches because the treatment of cancer has been superseded by precision medicines that target specific disease characteristics, promising maximum clinical efficacy, minimal safety concerns, and reduced economic burden. The introduction of next-generation sequencing technologies and the rising number of large-scale tumor molecular profiling programs across institutions worldwide have revolutionized the field of precision oncology. Molecular profiling of tumors has now become a routine and integral part of diagnosis, prognosis, and treatment planning for patients with advanced malignant cancers. Example ESR1 mutations are acquired most frequently when aromatase inhibitors are used to treat advanced breast cancer, POLE mutation are associated with increased expression of PD-L1/PD-1 in endometrial cancers, use of PARPi + Bevacizumab in firs line treatment for HGSOC, HRD positive and homozygous deletion of CDKN2A/B is associated with poor prognosis within IDH-mutant astrocytoma. This presentation will summarises the updated approaches in precision cancer medicine.

Accreditation On Molecular Laboratories
Sayyidi Hamzi
Reference Specialised Laboratory, and a Research, Development and Innovation Manager at Premier Integrated Labs Sdn Bhd.

Molecular diagnostics (MDx) is the rapidly developing area of laboratory medicine that investigates human, viral and microbial genomes. MDx techniques and platforms are playing a larger and more critical role in all areas of anatomic and clinical pathology. The quick emerging of the several targeted therapies and the concept of personalised medicine underlie the necessity to develop and to well organize a molecular pathology unit of high quality. One and key of the priorities in laboratory medicine is improvement of quality management system for patient safety. Quality in the health care is tightly connected to

the level of excellence of the health care provided in relation to the current level of knowledge and technical development. Accreditation is an effective way to demonstrate competence of the laboratory, a tool to recognize laboratories world-wide, is linked to periodical audits, to stimulate the maintenance and improvement of the quality, which leads to high standard of services for clients. This presentation is to describe the main steps to set up molecular laboratories based on ISO 15189.

Molecular testing in Hospital Kuala Lumpur

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Traditional pathology concentrates on the morphological manifestations of disease. There has been dramatic increase in knowledge of the molecular genetics of cancers over the last few decades and already we have reached the point where this can be translated into clinical application. These discoveries in research are being incorporated into the clinical setting with increasing rapidity and molecular medicine is transforming modern clinical practice, from diagnostics to therapeutics. This transformation is also deeply changing the way we practise pathology. Over the last few years, Histopathology Unit, Hospital Kuala Lumpur (HKL) has started its work in providing some molecular tests for solid tumour cancers such as breast cancers, gliomas, colorectal cancers, paediatric and soft tissue tumours. The molecular tests are integrated with other diagnostic tools in routine practice such as immunohistochemistry to understand the role of different gene expression in disease aetiology, provide more accurate means of diagnosis and more individualized approaches to therapy. The future histopathological findings will increasingly be combined with molecular pathological results as the future is morphology and molecular.

2. Chemical Pathology

Application of Whole Exome Sequencing in Inherited Immune Disorders

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Primary immunodeficiency diseases refer to inborn errors of immunity (IEI) that affect the normal development and function of the immune system. Prevalence of IEI in Malaysia is unknown. The estimated prevalence of 0.37 IEI cases per 100,000 population in Malaysia suggests under-reporting when compared to a prevalence of 1.1–7.5 per 100,000 population in other countries. The phenotypical and genetic heterogeneity of IEI have made their diagnosis challenging. Hence, whole-exome sequencing (WES) was employed in the pilot study to identify the genetic aetiology of 30 paediatric patients clinically diagnosed with IEI. Patients with clinical suspicion of IEI were recruited by Institute for Medical Research, from government hospitals across Malaysia. We identified causative variants in 14 patients using WES, amounting to a diagnostic yield of 46.7%. The median duration from age of onset to recruitment for WES was 4 years (Figure 3). Autoinflammatory disorders (n = 3), diseases of immune dysregulation (n = 3) and defects in intrinsic and innate immunity (n = 3) were the most common disease categories in our study cohort. Two categories, namely predominantly antibody deficiencies and combined immunodeficiencies with associated and syndromic features, were detected in two patients each. Only one patient was diagnosed with an immunodeficiency affecting cellular and humoral immunity. WES findings differed from the provisional clinical diagnosis in seven of the 14 cases (50.0%). Fifteen causative variants harboured in 13 genes were identified: namely, *SH2D1A, PIK3CD, NOD2, IL17F, STAT1-GOF, IL12RB1, STAT3-GOF, NFAT5, PNP, IL2RG, COPA, NLRC4-GOF, CD79A and STAT3-LOF*. This is the first study to determine the genetic aetiology of IEI in Malaysian paediatric patients using WES, which illustrates the complexity of diagnosis in patients with heterogenous clinical features and reaffirms for WES to be used in the diagnosis of IEI.

Serum Her2/neu and metastatic breast cancer

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HER2/neu is a transmembrane receptor belonging to the EGFR family which is overexpressed in up to 30% of breast tumours. Its external domain is cleaved and can be measured in the serum, making it a specific tumour marker. Elevation of serum HER2 is associated with poorer survival rates, higher tumour burden and disease recurrence. It is also elevated in over 2/3 of metastatic breast disease regardless of the histological/molecular status of the primary tumour. For this reason, serum HER2 is used to predict metastasis and concentrations correlate with the site of metastasis and number of metastatic sites. Nevertheless, it is not a surrogate for HER2 tumour status and may also be elevated in liver diseases and other tumours especially those with liver metastases. As current literature is contradictory, more research is required on the clinical utility of serum HER2 in breast cancer management.

Diagnosis of Inborn errors of metabolism (IEMs) and rare genetic disorder

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Inborn errors of metabolism (IEMs) are a heterogeneous group of about 1,500 disorders caused by pathogenic variants in genes coding for proteins such as enzymes and transporters that function in cellular metabolism. IEMs are individual rare but collectively common. A recent updated classification of IEMs proposes three large categories based on the size of molecules ('small and simple' or 'large and complex') and their implication in energy metabolism. Disorders of small molecules are linked to an excess or a deficiency of small diffusible water-soluble molecules can be diagnosed easily and rapidly by

measuring metabolites including amino acids, organic acids, acylcarnitines, porphyrins, fatty acid, purines, pyrimidines, neurotransmitters, etc by specific biochemistry methods. Energy related defects are IEMs with symptoms due, at least in part, to a deficiency in energy production or utilisation. Defects could be located in the cytoplasm or mitochondrion. Some of them are diagnosable with biochemical tests (lactate, amino acids, organic acids, creatine, enzymes assay, etc.). However, many of them lack the classical biomarkers and require molecular tests. Disorders of complex molecules are subdivided into 2 groups. Catabolic defects lead to storage of abnormal compounds which are detectable using biochemical methods. The disorders of synthesis, remodelling and trafficking, of complex molecules are more challenging to diagnose, often needing molecular tests. In summary, although biochemical tests remain the important way to diagnosis classical IEMs, molecular testing has recently revolutionized the diagnostic approach of many IEMs.

MicroRNAs in diabetic kidney disease

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Diabetic kidney disease (DKD) is the leading cause of end stage kidney disease (ESKD) worldwide. Currently, biomarkers of DKD lack sensitivity and specificity and despite advancement in treatment, disease progression remains. Thus, there is a need to further explore the underlying mechanisms of DKD in search of better diagnostic and therapeutic targets. The pathogenesis of DKD is multifactorial, involves activation of intracellular signaling pathways and ultimately culminates in kidney fibrosis. Epigenetic modification has been implicated in the early stages of DKD, its self-perpetuation and the phenomenon of metabolic memory. One of the emerging epigenetics is a family of small non-coding RNAs, known as microRNAs (miRNAs), which act as post-translational regulators of gene expression by binding to their mRNA targets. Owing to their unique characteristics, such as the ability of each miRNA to target several mRNAs and their easy access, circulating miRNAs has garnered much interest as novel clinical targets. Previously reported dysregulation of circulating miRNAs suggests their potential pathological roles in DKD. A local study profiling miRNAs in patients with DKD was recently done in Malaysia. Upregulation of several miRNAs with significant associations with routine clinical parameters were shown and predictions of their mRNA targets were achieved via bioinformatics analysis.

Precision Medicine in Metabolic Disorders

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The heterogeneity of drug response and susceptibility to adverse effects poses challenges in delivering optimal therapeutic outcomes to patients. Precision medicine represents a transformative approach that improves treatment accuracy, ensuring the intended therapeutics reach patients while minimizing adverse reactions. However, the complexity of managing metabolic disorders alongside other underlying medical conditions hinders the maximization of therapeutic delivery, emphasizing the need for precision medicine. While pharmacogenomics complements gene therapy development, it alone may not fully elucidate the variability of drug response and adverse effects. Therefore, the integration of pharmacometabolomics and pharmacometrics data becomes crucial in embracing the concept of personalized medicine. Pharmacometabolomics focuses on studying the metabolic profiles of individuals, identifying biomarkers that can predict drug response and adverse effects. On the other hand, pharmacometrics employs mathematical and statistical models to optimize drug dosing and individualize treatment plans based on drug concentration, pharmacokinetics, pharmacodynamics, and patient characteristics. There is a pressing need for innovation and high-throughput technology to address treatment failures and accelerate the development of precision medicine. These advancements enable efficient analysis of vast amounts of data, facilitating the identification of novel biomarkers and the development of targeted therapies. The global demand for precision medicine underscores the urgency to harness innovation and technology to improve patients' quality of life. In conclusion, the heterogeneity of drug response and susceptibility to adverse effects calls for the adoption of precision medicine. By embracing innovation and high-throughput technology, we can address treatment failures and expedite the development of precision medicine, ultimately benefiting patients worldwide.

A Metabolomic Approach to Identifying Potential Signature Biomarkers among Community-Dwelling Older Adult: From the Cognitive Function Perspective

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Ageing has been associated with neurodegenerative diseases and in particular irreversible dementia and ageing-related neurodegenerative diseases will become the 2nd leading cause of death after cardiovascular disease. Department of Statistics Malaysia (2022) has reported that 3.6 million or 11.1% of the Malaysian population are older adults aged 60 and above in 2022. Human aging is a highly complex biological process exhibiting great individual variation and until now, its metabolic basis has been little understood. 1H-Nuclear magnetic resonance (1H-NMR)-based urine and serum metabolomics profiling was conducted to identify metabolites which specifically representing a signature marker. Classification of different groups were analysed based on cognitive functions, physical functions, different intervention and characterisation were made based on multivariate statistical analysis including principal components analysis (PCA) and partial least-squares discriminant analysis (PLS-DA). Our findings lead to further analysis on other lifestyle components such as frailty with metabolites among older adult. These demonstrated that a metabolomic approach is useful for identification of metabolites that can act as potential signature biomarkers of successful aging.

Precision Medicine in Hypertension
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Hypertension (HT) affects ~1.4 billion adults worldwide. In Malaysia, >30% of the adult populations are hypertensive. Treatment of HT and its sequelae causes a significant burden to the healthcare expenditure. To avoid persistently growing burden, it is crucial to implement strategies that will improve the management and control of HT. Currently the primary strategy to manage HT is via pharmacological intervention. However, more than half of the treatment fails to achieve control of BP. One explanation to the variability responsiveness towards anti-HT medications is unable to identify the intermediate phenotypes of HT thence the inability to match the HT to specific medications and predict to which medication that a patient is most likely responding. Pharmacogenomics is the current leading candidate to operationalize precision medicine - if its findings are validated, it can be translated very quickly and efficiently to the bedsides. Using such genetic-guided approach, clinicians would be able to predict patient's response to a selected medication, thus avoiding the current trial an error in the management of HT. However, whilst there are ongoing pharmacogenetic clinical trials globally, several factors should be considered before translating these trials into clinical practice in Malaysia: (i) reproducibility of the genetic association signals; (ii) commonality of the candidate genetic variants in our diverse populations; (iii) functionally validation on the underlying pathophysiologic mechanism(s); and (iv) deep phenotyping of the HT subtypes. Collectively in this presentation, I shall revisit the current scenario of genetic study of HT in Malaysia, and the challenges in pursuing precision medicine of HT in Malaysia.

3. Forensic Medicine

Forensic Odontology: Role in Mass Disaster
Aspalilah Binti Alias
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In cases of a massive disaster, when it is difficult to identify victims, forensic odontology is essential. It involves applying dental knowledge to identify human remains using dental records, dental evidence, and dental examinations. The identification of individuals can be established through dental records, including dental X-rays, charts, and images. To identify a person's remains, forensic odontologists compare the dental records of missing people with the dental characteristics of the found remains. Even in catastrophic disasters, such as fires or explosions, teeth are very resistant to damage and often remain undamaged. The part of the human body that is most indestructible is the tooth. They not only exist after death but also remain unaltered for many thousands of years. Antemortem dental data are obtained from the missing person's by forensic odontologists. These records provide information about dental conditions that are absent, dental restorations, and other dental characteristics. They can establish certain identifications by comparing the information with postmortem dental findings, such as dental records and X-rays. In conclusion, to coordinate their involvement in mass disaster investigations, forensic odontologists collaborate closely with other forensic specialists, such as forensic anthropologists, pathologists, DNA experts, and law enforcement organizations. The integration across multiple forensic specialties is made possible through this collaboration, which ensures a thorough approach to victim identification.

Radiological Investigation of NAI
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Non- accidental Injury (NAI) or child abuse refers to all forms of physical and / or emotional injuries including sexual abuse resulting in actual or potential harm to the child's survival, health, development and even dignity. The incidence of such cases is on the rise and there is mandatory reporting of these cases. This is where radiologists, both Forensic and Pediatric radiologists play an important role together with other physicians in diagnosing such cases so that early intervention can be implemented in order to protect the child and any others siblings. However, differentiation of these findings from normal variants and underlying pathologies on imaging is very important to avoid wrongly accusing a caregiver of child abuse.

Management of Complicated Forensic Cases
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Although sudden unexplained deaths in the young are relatively uncommon, these deaths have tremendous impact on both lay and medical communities. Many sudden deaths in the young can be explained by cardiovascular abnormalities identifiable at autopsy, including myocarditis, cardiomyopathy and congenital coronary artery anomalies. However, nearly half of these sudden deaths involve previously healthy children with no abnormal findings at autopsy. Hence, it requires more tedious and comprehensive forensic investigations to exclude low-probability allegations. This presentation will describe how a routine case of sudden death in a young boy became complicated and poses special challenges to the forensic pathologist.

Myocarditis
Fazarina Mohammed
Department of Pathology, University Kebangsaan Malaysia, Kuala Lumpur.

Myocarditis is the inflammation of the heart muscle. To date, there is no definitive method in diagnosing myocarditis as a cause of death in autopsy, although there are guidelines for diagnosis in endomyocardial biopsy specimens. The talk will discuss on gross features and microscopic findings of myocarditis, and how to establish the diagnosis in autopsy. Molecular methods such as 16 rRNA next generation sequencing can be used to identify the causative agent for myocarditis.

Managing Disaster: Local DVI Setting in Humanitarian Context
Khoo Lay See
National Institute of Forensic Medicine, Hospital Kuala Lumpur.

Managing mass disasters involving multiple deaths are not uncommon among forensic practitioners. In fact, there are various definitions of disaster depends on the purposes, interests or the role of the definer, particularly in the field of forensic medicine. Irrespective of the differences in terminology, an interventional protocol called Disaster Victim Identification (DVI) is performed on all victims including identification and establishing cause of death for legal, humanitarian and compassionate reasons so that they can be returned to their families. Methods of identification used in cases of disasters should be scientifically sound and reliable whereby at present, the primary means of identification according to INTERPOL are friction ridge analysis, comparative dental analysis and DNA analysis. However, there is a need to depart from conventional thinking and understand the basis of the dynamic and evolving identification process whereby information flows from the usual antemortem and postmortem phase cannot be treated unidirectionally. It is also timely to think out of the box beyond dental records or DNA profiling as the only best technique in DVI, particularly in identification as a whole. The presentation highlights some international legal frameworks which contain obligations to the missing and the dead in armed conflicts, enforced disappearance and disasters as well as the origin of the Humanitarian Forensic Action (HFA). Application of HFA in local DVI operations is illustrated and it is envisaged that any smallest effort provided in the local forensic institution's capacity for the dead and their living families are part of the humanitarian consideration.

Sudden Infant Death Syndrome (SIDS): Malaysian Perspectives
Nur Ayutimasery Binti Abdullah
Department of Forensic Medicine, Hospital Tengku Ampuan Rahimah, Klang, Selangor.

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant younger than one year of age that remains unexplained after a thorough investigation. The Government of Malaysia, through the Ministry of Health (MOH) is committed in achieving the World Health Organisation's Sustainable Development Goals (SDGs) and Universal Health Coverage (UHC). Reducing child mortality and improving the well-being of children has always been part of the national development goals. The Family Health Development Division (FHDD) in MOH had developed The Stillbirth and Under-5 Mortality Reporting (SU5MR) System in 2012. The system ensures all under 5 deaths are to be investigated thoroughly including post mortem investigation on the deceased bodies. Through these cases of SIDS were captured and the incidence rate of SIDS according to districts in Selangor state currently stands at 0.7-1.5 per 10,000 live births. This talk intends to give an overview on how some of these cases came to the diagnosis of SIDs, i.e looking into the completeness of the investigations to arrive at the diagnosis of SIDS. This talk will also briefly touch on scene visits, classical features present and laboratory investigation taken to aid in arriving at the diagnosis.

Management of Complicated Forensic Cases
Muhammad Uzair Ahmad Suriani
Hospital Queen Elizabeth, Kota Kinabalu, Sabah. Born in Batu Pahat, Johor.

Every forensic pathologist should give full attention and thorough examination to any investigated case regardless of its public attention. However, we do realise that complicated or high-profile cases require more careful and extensive preplanning. Such cases have put us under tremendous pressure and affect our daily work and life. This is a sharing of a case on how we manage a complicated case with all the considerations taken before hand and subsequently on how to put ourselves at ease when handling with such cases.

Histopathological Findings of DAI
Wong Kum Thong
Department of Pathology, University of Malaya and Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia.

DAI or diffuse axonal injury is strictly speaking, a clinical syndrome that is used to describe immediate and prolonged coma in the absence of an intracranial mass lesion or diffuse metabolic change. Traumatic axonal injury is the pathological term where the key feature is axonal damage in various parts of the brain, especially the cerebral hemispheres, brainstem and cerebellum following rotational acceleration. Three grades of DAI are often used to describe the increasing severity of this condition. Although in some instances brain MRI may be useful, autopsy brain examination is still the gold standard for its diagnosis, especially with the application of beta amyloid precursor protein immunohistohemistry. This lecture will focus on macroscopic and microscopic features of DAI to aid the forensic pathologist in its recognition and diagnosis.

4. Genetic Pathology

Genetics of childhood epilepsy
Ahmad Ritthaudin Mohamed
Hospital Tunku Azizah Kuala Lumpur.

The past decade has seen tremendous advancements in genetic testing, and to lesser extent genetic treatments for childhood epilepsies. Many clinicians are grappling to cope with the progress, while for others, availability of genetic testing remains limited. Which patients should be tested? What tests do you send for? What if the results come back negative? Are there specific treatment for this genetic condition? These are just a few questions that are commonly thought of when managing a child with unexplained epilepsy. In this talk, I will share our own (limited) data on the genetics of severe, early onset epilepsies in childhood and highlight a few new developments in this area.

Cytogenomics in Haematological Malignancies
Chin Loi Khim
Department of Pathology, University Malaya.

Over the years, innovative technical advancements in the field of cancer cytogenomics have greatly enhanced the detection ability of chromosomal aberrations. This have paved the way in our understanding and delineating the relationship between clonal evolution and disease progression of cancer cells. Certain recurrent cytogenetic aberrations are closely associated with clinically or morphologically distinct subsets of leukemias or lymphomas. Cytogenetic analysis has an immense role in the diagnosis, risk stratification and treatment approach of haematological malignancies. It is especially useful in identifying complex karyotypes and defining clonal evolution and heterogeneity from single cell level analysis. Fluorescence in situ hybridization (FISH) techniques is able to complement conventional cytogenetics in the identification of cryptic chromosomal rearrangements that are undetermined by karyotyping. Remarkably, cancer cytogenomics have been instrumental in improving the care of patients with haematological malignancies, and has led to the emergence of molecularly targeted therapies in the field of precision medicine. The traditional boundary between cytogenetics and molecular genetics is blurring as technologies that are more sophisticated emerge. The future of cytogenetics is to constantly innovate and be an accompaniment to newer techniques.

Biomarker Testing in Malaysia: Enhancing Precision Oncology with Comprehensive Gene Profiling and Liquid Biopsy
Leong Chee Onn
International Medical University, Malaysia.

Precision oncology in Malaysia has reached a pivotal juncture, underscored by the integration of Next-Generation Sequencing (NGS) techniques. Traditional small panel testing and PCR assays, which offer a narrow view by targeting specific genomic loci, are now juxtaposed against comprehensive gene profiling facilitated by NGS. Liquid biopsies, utilizing circulating tumor DNA (ctDNA) from body fluids and their non-invasive nature permit dynamic surveillance of the tumor's genomic profile, offering insights into clonal evolution, minimal residual disease detection, and the emergence of therapeutic resistance alleles. Moreover, they hold potential for early detection by capturing genomic signatures even before clinical manifestations. Economically, the paradigm shift towards these advanced methodologies might initially present with higher costs. However, the long-term value proposition lies in therapeutic precision. By identifying actionable mutations, selecting targeted therapies, and modulating treatments based on real-time genomic surveillance, there's potential for increased treatment efficacy, reduced side-effects, and minimalized unnecessary interventions. In conclusion, the integration of comprehensive gene profiling via NGS and the utilization of liquid biopsies are setting the stage for a new era in Malaysian oncology. This advanced approach facilitates a more nuanced, timely, and cost-effective therapeutic strategy, furthering the goal of personalized cancer care.

New Perspective in Metastatic Breast Cancer
Mastura Md Yusof
Oncology Services, Pantai Hospital Kuala Lumpur and Subang Jaya Medical Centre.

We have been trying to treat breast cancer aggressively for decades. There is no other disease that has brought into being an entire industry of research organizations, oncologist surgeons and pathologists, like breast cancer. Positive progress in its outcome o ccurred as a result of intensive research and the advent of highthroughput technology tools that have expanded the classification of breast tumors into different molecular subtypes according to its gene expression profiles. They knowledge about their predictive and prognostic roles can enhance therapeutic strategies. The types and course of treatment varies from patients to patients depending primarily on the type and stage of cancer. Oncologists must also determine patient's physical fitness and organ function status for tolerability of the recommended therapy and avoid giving a drug that may exacerbate any existing toxicity. We will discuss new perspectives in breast cancer treatment that has brought about profound progress and improvement in patient outcomes from cancer such as prolongation of life, cure and quality of life improvements.

BRCA & BRCA-ness revisited
Roziana Ariffin
Premier Integrated Labs. Sdn Bhd and Sunway Medical Centre.

BRCA1 and–2 are components of the homologous recombination pathway of DNA repair required to effectively repair DNA double strand breaks. Patients with inherited BRCA mutations have an increased cancer risk. BRCAness on the other hand are cancers with defect in non BRCA DNA repair genes resulting in a phenotype mimicking mutations of germline BRCA1 and/or BRCA2 DNA repair gene that are involved in all phases of the cell cycle ultimately resulting in homologous recombination defciency(HRD). Deficiency in Homologous Recombinant related genes (RAD51, RAD54, DSS1, and RPA1), DNA damage signaling genes (ATR, ATM, CHK1, CHK2, and NBS1), or Fanconi anemia–related genes (FANCD2, FANCA, and FANCC) were shown to have sensitivity to PARP inhibitors. In other words, cells acquire BRCAness either by genetic inactivation of the BRCA or HRD genes. While generating BRCAness/HRD cells is experimentally straightforward in terms of molecular functions of BRCA1, BRCA2, and HRD proteins, the challenge is to identify bona fide BRCAness /HRD tumors clinically based on mutations, DNA copy scores, BRCA1 promoter methylation, RNA-seq metagene signatures, and functional assays. BRCAness concept improve our understanding of DNA repair, genomic instability, and mechanisms of action and use of PARP inhibitors and DNA-targeting agents. BRCAness defects are commonly present in multiple cancer types as BRCA1/2 defects in breast and ovarian cancer. Therefore, it opens a possibility to further test the potential of expanding PARPi therapy from breast and ovarian cancer to more cancer types with BRCAness features. Based on the sum of the BRCAneass features in each cancer type, published data suggests at least 21 cancer types as the potential targets for PARPi therapy: adrenocortical carcinoma, bladder urothelial carcinoma, brain lower grade glioma, colon adenocarcinoma, esophageal carcinoma, head and neck squamous carcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, mesothelioma, rectum adenocarcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, sarcoma, skin cutaneous melanoma, stomach, adenocarcinoma, uterine carcinosarcoma, and uterine corpus endometrial carcinoma.

This review also focuses on Pantai Premier Pathology experience in patient testing of BRCA & BRCAness genes ie genes associated with Homologous Recombination deficiency.

Liquid biopsy - Challenges and Emerging opportunities
Roziana Ariffin
Premier Integrated Labs. Sdn Bhd and Sunway Medical Centre.

Liquid biopsies had proven its ability to inform treatment selection at diagnosis, monitor clonal evolution during treatment, sensitively detect minimum residual disease following local control, and provide sensitive posttherapy surveillance. Advantages include reduced procedural anesthesia, molecular profiling unbiased by tissue heterogeneity, and ability to track clonal evolution. Traditional diagnostic measures require invasive procedures such as tissue excision using a needle, an endoscope, and/or surgical resection which can be unsafe, expensive, and painful. Additionally, the presence of comorbid conditions in individuals might render them ineligible for undertaking a tissue biopsy, and in some cases, it is difficult to access tumours depending on the site of occurrence. Being non-invasive liquid biopsy can now identify biomarkers for early diagnosis and targeted therapeutics. Liquid biopsies hold tremendous promise in oncology, enabling noninvasive serial surveillance with adaptive care.
Recent advances in technologies and bioinformatics have improved applicability in cancer landscape. This review also focuses on Pantai Premier Pathology experience i.e challenges & opportunities in liquid biopsy patient testing over the years.

How genetics/ genomics influence prostate cancer management
Tan Guan Hee
Sunway Medical Centre.

Prostate cancer is one of the commonest cancers in men. We are beginning to understand how certain genes and genetic mutations can affect the course of this disease. This presentation aims to outline the role of genetic testing in the management of prostate cancer. Numerous genetic tests have been developed for applications at various stages of the disease. Genetic tests could aid clinical decisions and help us improve treatment outcomes. However, the high costs of testing and limited access to certain tests might inhibit their widespread adoption in clinical practice. We should offer and discuss with our patients whenever genetic tests could impact on the direction of their treatment.

Congenital anomalies and genetic counselling in the genomics era
Thong Meow Keong
University of Malaya Medical Centre.

Congenital anomalies are defined by the World Health Organisation (WHO) as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life. It is also commonly referred to as and is interchangeable with birth defects, congenital disorders or congenital malformations. Congenital anomalies may occur as single or multiple defects, which may be part of a well-described association or syndrome. These require medical or surgical treatment, have serious adverse effect on health and development, or may have significant cosmetic impact on the child.

Recent advances in diagnostic technology in genomic medicine such as next generation sequencing and transcriptomics had enabled rapid diagnosis in patients with congenital anomalies and ‘unknown syndromes’. Genomic medicine is defined

as ‘‘an emerging medical discipline that involves using genomic information about an individual as part of their clinical care and the health outcomes and policy implications of that clinical use’’ (National Human Genome Research Institute [NHGRI]). While the focus is on these exciting new frontiers, there is an urgent need to address the issue of delivery of genomic medicine towards the healthcare of the population, namely the provision of genetic counselling to the affected individuals and/or their families.

There are genuine concerns that advances in genomic medicine will create an acute shortage of qualified genetic professionals with competency to practise safely in this field. In addition, some medical practitioners advocated that with the use of genomic technology, genomic testing should be available as a part of ‘routine’ patient testing repertoire. This lack of understanding of genomics in healthcare raised the question on the role of genetic and genomic counselling provided by medical practitioners and the steps needed to overcome these challenges.

Typically, genetic counsellors work with clinical geneticists and clinical scientists with the focus on providing information, interpreting genetic information to patients and to provide support and care for the patients and their families. In recent years, the scope of genetic counselling expanded to include interpreting variants, arranging complex genomic testing, assessing patients for appropriate disease screening and handle all the consequent psychosocial and ethical issues raised. Many have also taken on tasks which evolved into research, policy, education and more recently mainstreaming the genomic advances.

Lung Cancer and Biomarker Testing - Challenges and the Way Forward
Liam Chong Kin
University of Malaya, Kuala Lumpur, and University Malaya Medical Centre and UM Specialist Centre.

In recent years, lung cancer has moved to the forefront of the 2 most important trends in medical oncology - namely, targeted therapy and immunotherapy. Current guidelines recommend predictive biomarker testing before initiating first-line therapy in patients with advanced non-squamous NSCLC. The activating genetic alterations to be tested have expanded beyond *EGFR*, *ALK* and *ROS1* to include $BRAF^{V600E}$, *MET, RET*, *NTRK*, $KRAS^{G12C}$, *EGFR exon 20 insertion and HER2*.

In the real-world, guidelines-recommended biomarkers are often not tested leading to suboptimal use of targeted therapies. Community-based practices must send out tissue specimens for analysis, resulting in long turnaround times that could delay the start of therapy. The adoption of reflex molecular testing, in which a pathologist automatically orders the required tests on confirmation of a non-small cell lung cancer (NSCLC) histology results in a shorter turnaround time. Exclusionary testing, involving upfront testing for the more common *EGFR* and *ALK* alterations, followed by targeted next-generation sequencing panel multi-gene testing for the less common actionable genomic alterations is more cost-effective and tissue conserving. However, in a resource-limited healthcare environment, pulmonologists and oncologists must determine which biomarkers to prioritise for patients with lung cancer. Regulatory drug approval, local drug availability and access as well as availability of tests particularly for emerging biomarkers are challenges that complicate decision making. Other factors that impede biomarker testing include gaps in knowledge among healthcare providers, the often-limited quantity of tumour tissue for patients with advanced-stage NSCLC and reimbursement/insurance coverage which is a key determinant of drug and testing availability.

5. Haematology

Clot Wave and Its Utility in Clinical Disorders
Eusni Rahayu Md Tohit
Department of Pathology, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia

Clot wave (CW) analysis (CWA) or clot curve (CC) analysis (CCA) are parameters available in selected haemostasis analyzer. It provides extended information using routine coagulation specimen. The first part of the talk will focus on the principle and parameters available in CWA/CCA such as first and second derivatives which corresponds to acceleration and velocity of clot formation. Other extended parameters will also be discussed. The second part of the talk will be literature reviews on utility of clot wave in various clinical disorders such as in diagnosis and monitoring of haemostasis disorders following treatment /blood products utilization, patterns of CW/CC in diseases such as disseminated intravascular coagulation, inherited bleeding disorders, extended parameters patterns in selected population such as pregnant ladies. Potential research of CW/CC in clinical disorders covering diagnosis, monitoring and pattern of CW/CC will also be discussed.

Genetics in haemostasis
Faraizah Dato’ Abdul Karim
National Heart Institute and private laboratories in Kuala Lumpur.

Blood clotting formation involved in hemostasis are very complex and involve interplays between platelets, coagulation, and fibrinolysis. This process involves a series of orderly steps including components of the vasculature, platelets (primary haemostasis) and coagulation proteins (secondary haemostasis), leading to the formation of a platelet plug and culminating in the formation of a stable fibrin clot. Genetic variants in genes that encode for these proteins are known to cause inherited forms of bleeding or thrombosis.

Inherited bleeding disorders have a wide range of frequencies from 1 in 1000 live births for von Willebrand disease (VWD) and 1 in 5000 males for hemophilia A as most common inherited bleeding disorders or to just a handful of cases for many ultra-rare platelet disorders. Venous thrombosis has an overall annual incidence of about 1 in 1000 and is caused by environmental (lifestyle) effects, in association with genetic risk factors as compared to paediatric population with rates of about 1 in 100 000 due to mainly genetic factors.

The genes encoding clotting factors were among the first to be clone in the 1980s, and over the past 30 years, there has been an increasing application of this information into the clinical management of disorders of hemostasis and thrombosis. Molecular genetic diagnosis of bleeding disorders remains an important and integral part of the evaluation of this condition. However, before embarking on genetic testing, it is imperative that detailed clinical evaluation and conclusive phenotypic diagnosis be available. Genetic analysis are required 1.To confirm phenotypic diagnosis. 2. Risk of inhibitor development 3. To determine reliably female carrier status because the majority of female carriers have normal plasma eg.FIX:C levels. 4. Prenatal Diagnosis. 5. Phenotypic tests (often functional in nature) may be difficult to interpret eg subtypes of von Willebrand disease (VWD) such as 2B and 2M. 6. Rare inherited coagulation and platelet diseases

There are different approaches to the genetic evaluation of bleeding disorders: analysis of single nucleotide polymorphism (SNP) or microsatellite short tandem repeat (STR) markers in the gene of interest to track the defective chromosome in the family (linkage analysis), or identification of the disease-causing mutation in the patient's coagulation factor gene (direct mutation detection). With the availability of next generation sequencing technologies, wider application of genetic testing for inherited diseases of hemostasis can be determine.

HLA in Transfusion and Transplantation

Ailin Mazuita Mazlan
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Transfusion and transplantation of allogeneic cells and tissue is a challenge to the immune system. Human leucocyte antigen (HLA) that is present on the cell surface plays a crucial role in eliciting immune response from recognizing to eliminating the allo-antigen via cellular or humoral pathways. HLA alloimmunization is responsible for a number of transfusion adverse reactions. HLA matched graft is the key success in heamatopoietic stem cell and organ transplant.

This presentation will touch upon a brief overview of the HLA system and current methods for HLA typing and HLA antibody testings. Refractory to platelet transfusion is quite a common transfusion adverse reaction seen in hematological patients representing 5-14%. Anti-HLA is the commonest culprit in immune platelet refractoriness. Eventhough HLA matched platelet transfusion is the best treatment option for these patients, finding the matched donors are diffucult. This resorts to alternative treatment options such as antigen negative and crossmatched compatible platelet.

Transfusion related acute lung injury (TRALI) is another complication of transfusion that is caused by anti-HLA. Blood collection centers need to study the best and the most cost effective TRALI risk mitigation strategy to be implemented. The histocompatibility and immunogenetics laboratory facilitate transplanters in searching for a HLA matched graft donors. Transplanting against HLA barrier can be done successfully with the appropriate compatibility test and HLA antibody monitoring.

Lymphoma infiltration in the bone marrow trephine biopsy

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Lymphomas often result in bone marrow infiltration. The bone marrow involvement can be assessed through microscopic examination of bone marrow aspirates and trephine biopsy sections, flow cytometric immunophenotyping and molecular techniques. Bone marrow involvement varies according to subtypes of lymphoma. Among B-lineage lymphomas, bone marrow infiltration is more common in indolent lymphomas than in aggressive ones. It is more likely for B-cell lymphomas to have bone marrow infiltration compared to T-cell lymphomas. Lymphomatous infiltration of the bone marrow can be overt and easy to identify but, in some cases, it poses a challenge to differentiate neoplastic from reactive lymphoid infiltration. Flow cytometry undertaken on bone marrow aspirate samples is more sensitive than tissue-based immunohistochemistry study. However, approximately 2% to 7% of the time, attempts at bone marrow aspiration yield no fluid, resulting in the so-called dry tap. In histological sections of the bone marrow trephine biopsies, the pattern of the infiltration, cytological characteristics and immunohistochemistry studies are essential in confirming the presence of lymphoma infiltration and distinguishing it from reactive lymphoid infiltration or hematogones. Formulating differential diagnoses of lymphoma subtypes is aided by analyzing infiltration patterns, which also helps determine if infiltration is benign or neoplastic. In subtle interstitial infiltrates or in a very low-level infiltration by the lymphoma, immunohistochemistry stains and flow cytometric immunophenotyping are vitally important. Molecular evaluation to determine the clonality of the T-cell or B-cell present in the bone marrow trephine biopsy might also be useful.

The Evolving Role of Next-Generation Sequencing in Screening & Diagnosis of Haemoglobinopathies
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Hemoglobinopathies are highly clinically heterogeneous autosomal recessive hereditary blood disorders that frequently involve the inheritance of more than one abnormal gene. Traditionally, the definitive diagnosis involves labor-intensive, mutation-specific test designs due to the wide diversity of these disorders. Next-generation sequencing (NGS) has emerged as an alternative, more complete, and versatile molecular approach for thalassemia gene screening. Studies have demonstrated that NGS significantly improves thalassemia detection rates compared to traditional methods. It identifies a higher carrier rate and detects more carriers of both alpha and beta thalassemia. In this presentation, the role of NGS in screening, as well as pre- and post-natal diagnostics of hemoglobinopathies, and the added value of NGS will be presented based on the results described in the literature.

Interesting Cases in Hemostasis: From Diagnosis to Management
Lailatul Hadziyah Mohd Pauzy
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Hemostasis plays a vital role in maintaining the delicate balance between bleeding and clotting. Here we present a myriad of intriguing cases each presenting unique challenges in terms of diagnosis and management. The first case revolves around a 3-year-old boy who presented with fever and pallor. He was diagnosed to have Acute Myeloid Leukemia with concomitant acute infection of leptospirosis. Incidentally, he was noted to have isolated prolong APTT and further investigations reveal positive Lupus Anticoagulant antibody. We explore how these findings impact on the treatment and management of his condition. Next, we present a case of a 42-year-old lady with longstanding mild bleeding tendencies. Extensive investigation was done and a provisional diagnosis of platelet function disorder was given. We demonstrate how highly specialised testing, particularly the use of light transmission aggregometry and electron microscopy may aid in accurate diagnosis of platelet disorders. Finally, we present a case of a family with an extremely rare bleeding disorder of combined Factor V and Factor VIII deficiency. We discuss the pathophysiology and the common presenting features of this disease. This case illustrates why molecular diagnosis play a pivotal role in accurate and timely diagnosis of a rare bleeding disorder. Through these cases, the evolving landscape of hemostatic medicine becomes evident, emphasizing the significance of the multiple modalities of laboratory testing in aiding accurate diagnosis and management of hemostasis cases.

Inter-relationship and clinical implication of PNH in AA & MDS
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Aplastic Anaemia, Myelodysplastic Syndrome, and Paroxysmal Nocturnal Haemoglobinuria are associated with bone marrow failure. Traditionally these diseases have been understood as distinct diseases with contrasting pathophysiology. However, there are significant disease overlap in which the bone marrow is hypocellular in about 10% of MDS, resembling AA and, PNH cells can be detected in up to 5% of MDS and in more 50% of AA patients. Recent publications have shown PNH positivity in both diseases, at any clone size, is a good predictor of response to immunosuppressive therapy and of good outcome after HSCT. PNH positivity also have favourable impact on overall survival, with a dramatic reduction mortality even for clone size of 0.01%.

Molecular Immunohematology: Red cell genotyping
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The increasing awareness of the genomics revolutions has an important impact on transfusion medicine, as well as its potential application to change how blood is chosen for transfusion. To avoid immunising potential recipients or inducing a haemolytic transfusion reaction due to serology testing discrepancies, molecular immunohematology is required for comprehensive typing of donors and patients. In 2017, we introduced and performed molecular typing for donors or patients' samples, which enable blood groups to be determined when serologic findings are weak, unexpected, or unclear. Most antigenic polymorphisms are due to single nucleotide polymorphism changes in the respective genes, and DNA arrays that target these changes have been validated by comparison with antibody-based typing. Importantly, the ability to test for antigens for which there are no serologic reagents is a major medical advance to identify antibodies and find compatible donor units, and can be life-saving This presentation summarizes the evolving use and applications of genotyping for blood group antigens. Molecular typing has been proven to be an effective tool for assisting pre-transfusion testing in serology-based laboratories in our experience. The little blood volume needed for testing and eligibility for screening eligible donor blood in difficult cases or individuals with rare phenotypes are two advantages of molecular testing employing established PCR techniques. Molecular typing should be incorporated as one of the tools in the transfusion laboratory that performs complicated immunohematologic investigations.

Update in chronic myeloid leukaemia: Laboratory and clinical perspectives
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The discovery of targeted therapy in Chronic myeloid leukaemia (CML) has been a pioneer to the other discovery of novel mutation and treatment in haematology history. With the tyrosine kinase inhibitor (TKI), people living with CML started to have a hope to live longer. For the past 2 decades, TKIs have done a huge paradigm shift on CML treatment landscape. Currently, the aim of CML treatment is to achieve treatment free remission (TFR) by achieving as early as possible deep molecular response (DMR). The patient assisted programme in Malaysia (MyPAP) has been successfully helping people living with CML. Currently 2673 patients benefited from this programme in Malaysia and be able to access to imatinib mesylate and nilotinib. With TKI therapy, the challenges will be development of tyrosine kinase domain mutation (TKD) like T315I, G250E, E255K, M244V, M351T, and Y253F. On 10th September 2023, Asciminib the 3rd line therapy has been officially launched in Malaysia. Asciminib, a first-in-class allosteric inhibitor of BCR::ABL1 kinase activity, is now approved for the treatment of patients with chronic-phase chronic myeloid leukemia who failed 2 lines of therapy or in patients with the T315I mutation. With the advancement of CML treatment, ideally the laboratory monitoring of molecular response must comply with the clinical demand. However, the budget is always the limitation.

Minimal Residual Disease monitoring in Childhood Acute Lymphoblastic Leukemia
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Contemporary treatment protocols for childhood acute lymphoblastic leukemia (ALL) require assessment of Minimal Residual Disease (MRD) to assess response to chemotherapy and for risk stratification. The presence of minute numbers of blasts not visible via morphology i.e. MRD guides treatment decisions. Patients with a negative MRD at the end of remission induction may continue with standard or reduced-intensity chemotherapy, while those with higher MRD levels could benefit from targeted therapies, stem cell transplantation, or other innovative approaches to ensure better disease control. Various laboratory techniques are employed to detect and quantify MRD. These platforms include flow cytometry, polymerase chain reaction (PCR), quantitative PCR, digital droplet PCR and next-generation sequencing. Irrespective of the laboratory method used, MRD analysis remains a vital component in the management of childhood ALL. By detecting even trace amounts of leukemia cells at various treatment time-points, early intervention and personalized treatment approaches can be instituted for every patient.

Precision Medicine and Glucose-6-phosphate dehydrogenase (G6PD) deficiency
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Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a condition that affects the ability of red blood cells (RBC) to respond to oxidative stress, is the most prevalent enzyme deficiency globally. Loss-of-function mutations in the G6PD gene cause this disorder. Variable clinical manifestations of affected individuals are seen where they are more susceptible to oxidative stress leading to acute haemolytic anaemia (favism), and there may be wide inter- and intra-individual variability in the development of haemolytic crisis. Affected new-borns present with an increased risk of hyperbilirubinemia which can be severe with its sequelae of bilirubin neurotoxicity. Pathophysiology of jaundice in G6PD-deficient neonates is different from that of favism, as there is little evidence of hemolysis in these infants.

Family history, clinical findings, RBC morphology, and biochemical tests are well-recognized diagnostic tools, however, several confounders may further challenge the diagnostic workup. These include concomitant blood loss, nutrient deficiency and the coexistence of other haemolytic disorders.

WHO recommends screening for G6PD activity in all infants in countries with a high prevalence of this disorder and fluorescent spot test as a screening tool have been utilized despite the limitations. Molecular techniques, the most unambiguous method, are increasingly used and may be fundamental in unravelling the diagnosis including for compound heterozygous G6PD mutations. In this era of precision medicine, there is an increasing need to develop Point-of-Care Testing (POCT) with molecular genetic testing with the goal of establishing a risk stratification according to the WHO classification and better-informing healthcare providers about disease prognosis, enabling more comprehensive management strategy for patients.

Monitoring Post-Transplant (Chimerism)
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Chimerism means an individual with cell populations from genetically different individuals coexist. The word chimerism derives from the term “chimera”, a monster from Greek mythology that is part lion, goat, and serpent. Chimerism can occur either spontaneously, such as in the cases of feto-fetal transfer or feto-maternal transmission, or artificially in the case of allogeneic hematopoietic stem cell transplantation (HSCT). Nowadays, allogeneic HSCT is an efficient curative treatment approach for many hematologic diseases, but it also cause various complications, such as toxicity related to treatment, infections, recurrence of the disease, and immunological reactions including rejection of the transplantation by the recipient and graft-versus-host disease (GVHD). The success of allogeneic HSCT is evaluated by chimerism analysis, in which the monitoring

of the relative amount of living donor cells and residual recipient cells is performed in samples of peripheral blood or bone marrow following transplantation. Chimerism analysis is performed to evaluate the engraft status of the transplanted cells and the eventual recurrence of the disease. In addition, minimal residual disease (MRD) analysis can also provide significant prognostic information regarding relapse of disease, thus influencing clinical decisions. Previously, chimerism studies were based on phenotyping and cytogenetic techniques, such as fluorescence in situ hybridization (FISH), which can be applied only to sex-mismatched donor recipient pairs as a limiting factor for routine application. Subsequently, polymerase chain reaction (PCR) and fragments analysis were adopted to study VNTRs or STRs. In particular, STR analysis is considered the gold standard technology for chimerism monitoring after allogeneic HSCT, as specified in the EuroChimerism Consortium guidelines. Nevertheless, a sensitivity of around 1% of STR-PCR analysis may represent an obstacle for timely intervention. Other methods such as quantitative real-time PCR (qPCR), digital PCR (dPCR) and next generation sequencing (NGS) able to quantititate the chimerism and have sensitivity up to 0.01%, are deemed to represent the future of chimerism.

Role of Next Generation Sequencing in Acute Myeloid Leukemia

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Acute Myeloid Leukemia (AML) is a heterogenous clonal hematopoietic malignancies. In the early years, the diagnosis of AML is solely based on morphology. Over the last 20 years, the investigation of AML has improved according to WHO classification and European LeukemiaNet (ELN) prognostication in which it has integrated immunophenotyping and genetic features. Based on Surveillance, epidemiology and End Results (SEER) Database (USA), the 5-year survival rates have increased from 6.3% in 1975 to 28% in 2017. The outcomes of patients with AML showed incremental improvement due to the improvement in treatment stratification and targeted therapies.

The advent of next generation sequencing (NGS) technologies has expedited the discovery of novel genetic lesions in AML. The use of NGS techniques can detect mutations in the pre-treatment phase hence able to assess the risk of patient with AML, establishing prognosis, provide molecularly targeted option and monitor patients post treatment. The used of newly identified mutations, or in conjunction with previously characterized genetic anomalies has gained the prognostic insights. The therapy of AML has largely remained unchanged from the standard 3+7 regimen, for this reason the most important advances to current prognostic markers will be identifying gene mutation(s) that can prospectively stratify patients who will benefit from an allogeneic hematopoietic stem cell transplant (HSCT). National Comprehensive Cancer Network (NCCN) guidelines recommend stem cell transplant (SCT) for intermediate- to poor-risk patients with AML who are less than 60 years old. However, given the risks associated with HSCT, the identification of some genomic alterations in AML has a great potential for the incorporation of targeted therapies, generating a hope for further improvement in treatment outcome.

The NGS based AML sequencing will also provide insights on the pathogenesis of leukemia. Paired analysis of diagnosis and relapse samples have revealed some understanding in the genetic makeup of cells. A better understanding of the AML genome evolution is needed to help in understanding the mechanisms of relapse, improve the understanding of recurrent patterns of therapy resistance and suggest appropriate molecular targets.

6. Medical Microbiology

Molecular Characterisation of Dengue Viruses

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Malaysia experienced an unprecedented dengue outbreak from 2014 to 2016, resulting in a high number of fatalities. There is growing concern that the rise in dengue cases and the increased mortality may be attributed by viral factors. Therefore, our study aimed to molecularly characterize the dengue virus (DENV) to elucidate the viral factors contributing to dengue virus infection and severity during the 2014-2016 outbreak. We performed phylogenetic analyses to identify the pattern of dengue serotype and genotype distribution and used in-vitro infection assessment to measure replication efficiency of the virus. We found that DENV 1 genotype I was the predominant serotype and genotype in the studied outbreak. Additionally, dengue isolates from severe cases demonstrated slow but prolonged replication and infectivity kinetics, persisting up to day six in in-vitro infection assessment. In contrast, non-severe cases exhibit an early rise in replication and infectivity kinetics, followed by a decline in sustainability. Replication and infectivity kinetic trends also differ by dengue genotypes, consistent with the prevailing circulating genotypes. Involvement of sfRNA in disease severity is reflected in higher copy numbers among severe dengue isolates compared to non-severe isolates, particularly severe DENV 2 isolates. The data from this study demonstrated that viral factors, such as serotype shift, the re-emergence of specific genotypes, and an efficient replication and infectivity mechanism, collectively play a role in contributing to dengue outbreaks by enhancing viral fitness, survival, and disease severity.

A tale of two MRSA clones: The HCTM Chronicle
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The phenomenon of MRSA clonal replacement has been reported in many hospitals worldwide. Over the years, the growing number of CA-MRSA clones gaining dominance over formerly-dominant, established HA-MRSAs in hospital settings have been described. We performed molecular surveillance on MRSAs isolated in the years 2009 and 2017 in Hospital Canselor Tuanku Muhriz, where it was discovered that the dominant MRSA genotype of SCCmec III-SCCmercury (ST239-III) in 2009 has later been replaced with SCCmec type IV (ST22-IV) in 2017. We seek to elucidate factors associated with the clonal replacement via whole-genome sequencing (WGS) and phenotypic comparisons. Representative strains of the hospital from years 2005 – 2017 were included in this surveillance, antimicrobial stewardship activities and infection control policies during the surveillance period were also reviewed concurrently. We built the case for periodical surveillance of antibiotic resistant pathogens in hospitals, be it via antibiogram profiling, molecular typing, genome sequencing or phenotypic investigations

Application of Whole Exome Sequencing in Inherited Immune Disorders
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Primary immunodeficiency diseases refer to inborn errors of immunity (IEI) that affect the normal development and function of the immune system. Prevalence of IEI in Malaysia is unknown. The estimated prevalence of 0.37 IEI cases per 100,000 population in Malaysia suggests under-reporting when compared to a prevalence of 1.1–7.5 per 100,000 population in other countries. The phenotypical and genetic heterogeneity of IEI have made their diagnosis challenging. Hence, whole-exome sequencing (WES) was employed in the pilot study to identify the genetic aetiology of 30 paediatric patients clinically diagnosed with IEI. Patients with clinical suspicion of IEI were recruited by Institute for Medical Research, from government hospitals across Malaysia. We identified causative variants in 14 patients using WES, amounting to a diagnostic yield of 46.7%. The median duration from age of onset to recruitment for WES was 4 years (Figure 3). Autoinflammatory disorders (n = 3), diseases of immune dysregulation (n = 3) and defects in intrinsic and innate immunity (n = 3) were the most common disease categories in our study cohort. Two categories, namely predominantly antibody deficiencies and combined immunodeficiencies with associated and syndromic features, were detected in two patients each. Only one patient was diagnosed with an immunodeficiency affecting cellular and humoral immunity. WES findings differed from the provisional clinical diagnosis in seven of the 14 cases (50.0%). Fifteen causative variants harboured in 13 genes were identified: namely, *SH2D1A, PIK3CD, NOD2, IL17F, STAT1-GOF, IL12RB1, STAT3-GOF, NFAT5, PNP, IL2RG, COPA, NLRC4-GOF, CD79A and STAT3-LOF*. This is the first study to determine the genetic aetiology of IEI in Malaysian paediatric patients using WES, which illustrates the complexity of diagnosis in patients with heterogenous clinical features and reaffirms for WES to be used in the diagnosis of IEI.

***Helicobacter pylori* Antibiotic Resistance: Past, Present and Future**
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Helicobacter pylori is a gram-negative, spiral-shaped and microaerophilic bacteria that colonised more than half of the human populations. *H. pylori* infection causes chronic gastritis, peptic ulcer disease, gastric cancer and gastric MALT lymphoma. While the prevalence of infection has been shown decreasing over time in many parts of the world, the increase in antibiotic resistance has been reported in many countries. Antibiotic resistance in *H. pylori* substantially hinders the efficacy of eradication regimens. Various regimens have been used to eradicate the infection, which included a proton pump inhibitor or potassium-competitive acid blocker, plus two or three antibiotics. Amoxicillin, metronidazole, clarithromycin, tetracycline and levofloxacin are the most frequent antibiotics used in different combinations of eradication regimens. Resistance prevalence is dynamic and can greatly vary among countries over the years. Recent reports showed that there is a variation in the trends and evolution of *H. pylori* strains towards different antibiotics. Amoxicillin resistance generally exhibited no evolution. Metronidazole resistance exhibited different trends, including an increase, a decrease and no evolution. Clarithromycin and levofloxacin resistance increased in some countries, but remained stable in others. Tetracycline resistance was low and stable in most of the countries. A better understanding of the emergence and spread of resistant bacteria helps in the development of new drugs, improved diagnostic tools as well as optimising the available regimens. The advent of in silico approaches of bioinformatics provide an extraordinary advancement in the field of drug discovery. Novel and potential drug candidates can be rapidly screened using molecular docking and molecular dynamics simulations approaches that predict drug-receptor interactions. This paves the way for the development of a new anti-*H. pylori* agents to combat the antibiotic-resistance *H. pylori* strains.

Molecular Diagnostics of Nontuberculous Mycobacterium
Muhammad Nazri Aziz
Lablink (M) Sdn. Bhd.

The mycobacteriology testing algorithms involve various diagnostic methods such as microscopic examination of acid fast bacilli (AFB), culture, antibiotic susceptibility test, nucleic acid amplification tests (NAATs), MALDI-TOF, and sequencing. Traditional methods (staining of acid fast bacilli and microscopic examination) are still widely used by many laboratories as their first line diagnostic approach. New advances in molecular detection of Mycobacterium tuberculosis (MTB) and

Nontuberculous mycobacterium (NTM), including the faster and simpler NAATs, MALDI-TOF, and Next-Generation Sequencing (NGS), have resulted in a shorter time for diagnosis, and therefore faster and effective patients' management. Modernization of traditional mycobacteriology testing algorithms will be further discussed in this presentation. The difficulties and challenges of culturing, identification, and antibiotic susceptibility testing of the slow growing Mycobacterium marinum will be chosen as the story line.

Utilization of Pan-Fungal PCR From Direct Clinical Specimens in Resolving Clinical Diagnostic Dilemmas
Murnihayati Hassan
Bacteriology Unit, Infectious Disease Research Centre, IMR

Dr Murnihayati Hassan graduated with a medical degree and Bachelor of Biomedical Science from University of Melbourne, Australia, and received Master in Pathology (Microbiology) from Universiti Sains Malaysia in 2019. She has experience servicing as medical officer and as clinical microbiologist in North-eastern Malaysia and Perak state hospital. She is now a clinical microbiologist in Bacteriology Unit, Institute for Medical Research (IMR) since 2022. Her research interest is in antimicrobial resistance, leptospirosis, medical mycology and vaccinology. Apart from that, she is also a lecturer and mycology module coordinator for Diploma in Medical Microbiology under SEAMEO Tropmed Regional School, a committee member of the National Antimicrobial Resistance Committee and actively involved in the ISO Implementation Committee of IMR. She received awards in various conferences in the past, and has published her works in local and international journals.

The prevalence of invasive fungal infections (IFIs) is an increasing global health burden due to the growing number of immunocompromised and severely ill patients. Fungal culture is the gold standard for diagnosis of IFIs, but it is time-consuming and requires technical expertise for execution of the test. Timely targeted therapy requires rapid identification of the fungal pathogen together with antifungal resistant gene recognition. Pan-fungal PCR provides a rapid identification of fungal pathogens directly from clinical specimens targeting dual loci of ITS and TEF1α. Additionally, optimal accuracy is achievable using next generation sequencing (NGS) technologies that allow for high discriminatory analysis of genetic diversity applicable for outbreak investigation and for drug resistance characterization. To date, mycology interest groups are focusing on establishment of a standardized protocol for direct pan-fungal PCR testing through rigorous validation process. In conclusion, pan-fungal PCR is a promising and highly sensitive diagnostic test for identification of IFIs in highly suspect clinical cases. Clinical utility pan-fungal PCR has expanded fungal laboratory armamentarium. Result interpretation is recommended in combination with other diagnostic results relevant to the clinical context.

Adopting Molecular Diagnosis of Parasites Where It Fits
Raden Shamilah Hisam
Parasitology Unit, Infectious Disease Research Centre, Institute for Medical Research, Malaysia.

IMR is considered the National Reference Laboratory for Parasitic Diseases for Malaysia where the Parasitology Unit under the Infectious Diseases Research Center conducts parasitology tests that are of medical importance, ranging from microscopy, serology to molecular test methods. In this session, we will discuss reasons for selection of the diverse test methods and the move towards inclusion of molecular methods as routine tests. Examples of parasitic diseases such as Amoebiasis, Toxoplasmosis, Malaria and application of a variety of test methods for these diseases will be discussed. There are matters to consider when adopting molecular methods such as availability of trained staff, financial stability and adequate lab infrastructure. At the end of the day, it matters whether your laboratory will be designated as a peripheral or state or a national level laboratory where you then decide on the most appropriate tests to perform, regardless of low or high demand for such tests.

Structural Bioinformatics unveils insights in SARS-CoV-2 Susceptibility and Transmissibility
Su Datt Lam
Universiti Kebangsaan Malaysia

The COVID-19 pandemic has caused a substantial global impact on both public health and socioeconomic since its emergence in 2019. Many countries are still experiencing an intermittent rise in the number of infections due to the emergence of Variants of Concern (VOCs) within the SARS-CoV-2 virus. Despite the availability of vaccines, re-infection is common. In the early phases of the pandemic, we embarked upon an inquiry into the susceptibility of various animals to COVID-19 infection. The mechanism by which SARS-CoV-2 gains entry into host cells involves its spike protein (S-protein) binding to the ACE2 receptor. We modelled Spike protein: ACE2 complexes from vertebrate species and ectoparasites. We quantified changes in the energy of the complex caused by mutations in each species, relative to human ACE2, and correlated these changes with COVID-19 infection data.

Beyond the receptor binding domain of spike proteins, many VOCs are known to harbour novel mutations within the N-terminal domains of spike protein. Studies suggest that the N-terminal domain might have a role in facilitating virus entry via binding to sialic-acid receptor. We structurally characterized the sialic acid binding pockets, explored whether variants could enhance the binding to sialic acids and therefore to the host membrane, thereby contributing to increased transmissibility. Certain populations or clinical groups could exhibit an increased susceptibility to COVID-19. Whilst socioeconomic and cultural differences are likely significant important, human genetic factors could influence susceptibility. Experimental studies indicate SARS-CoV-2 uses innate immune suppression as a strategy to speed-up entry and replication into the host cell. In light of this, we employed a structural bioinformatics approach to analyse the impact of missense variants from human and viral proteins, utilizing the 3D structures of SARS-CoV-2: human protein complexes. Our studies demonstrate the power of bioinformatics in deepening the understanding of SARS-CoV-2. This information may be useful for vaccine/drug design.

Point-of-care rapid test for *Strongyloides stercoralis* infection – why the need and updates
Rahmah Noordin
Universiti Sains Malaysia.

Strongyloides stercoralis, which causes strongyloidiasis, infects about 600 million people worldwide, especially in tropical and subtropical regions. The autoinfection phenomenon of the parasite leads to almost life-long infection. When an infected person is immunosuppressed, the asymptomatic chronic infection can transform into fatal hyper- and disseminated infection. Thus awareness of this infection among doctors and the availability of a good rapid test is essential in patient management, especially in less developed areas. SsRapid® is a prototype point-of-care (POC) lateral flow cassette test that uses recombinant NIE antigen and specific IgG4 detection. The initial laboratory study using defined positive and negative serum samples showed a sensitivity of 97% and a specificity of 95%. Subsequently, it was evaluated in laboratory and field studies in several countries. They included comparisons with parasitological methods, commercial ELISAs, and real-time PCR. The samples were from patients (immunocompetent and immunocompromised), endemic area residents with and without other infections, and healthy individuals. Overall, the rapid test shows good diagnostic performance and is promising to fill the gap in the current need for a rapid test for *S. stercoralis* infection.

The Application of Pharmacokinetics/Pharmacodynamics Principles in Antimicrobial Stewardship Program
Zakuan Zainy Deris
Medical Microbiology and Laboratory, Hospital Universiti Sains Malaysia, and Department of Medical Microbiology and Parasitology at the School of Medical Sciences, Universiti Sains Malaysia.

Emergence of antimicrobial resistant organisms is a threat to global health security. The overuse and misuse of antibiotics are among major factors that contribute to this phenomenon. Antimicrobial resistance, together with the lack of effective antibiotics leads to increased mortality and morbidity due to the infection.

With limited active new agents in the treatment of MDR organisms, the optimal use of currently available antibiotics is important for effective killing of the pathogen prior to resistant development, as well as for treatment of low resistant organisms when there is no other antibiotic option. Choosing the optimal antibiotic regimen and dose includes considering the pathogen's MIC, site and severity of infection, the drug concentration and its influence factors, and antimicrobial determinants of bacteria killing. Thus, selecting the in-vitro active antibiotic alone is inadequate, and the application of pharmacokinetic/pharmacodynamic (PK/PD) concepts in antimicrobial prescription is equally important for optimal antibiotic use in AMS programs.

Dose optimization by the PK and PD principles background increases the likelihood of achieving the therapeutic concentration of antibiotics at infection sites. For the time-dependent killing activity antibiotics, the maximum bactericidal effect can be achieved with maximizing the time of drug concentration above MIC ($\%T_{>MIC}$), whereas for the concentration-dependent antibiotics, the maximum bactericidal effect can be achieved with maximizing the drug concentration above MIC (C_{max}/MIC). In case of mixed concentration- and time-dependent antibiotics, the maximum bactericidal effect can be achieved with maximizing the total drug amount with the time (AUC/MIC). Therefore, the application of PK/PD increases the chances of clinical success and reduces the development of resistance.

Abstracts of the oral and poster presentations are as follows:

1. Anatomical Pathology

AP1: Alveolar rhabdomyosarcoma of the left hand, rare presentation in young children with diagnostic challenges
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Introduction: Rhabdomyosarcoma is a highly malignant soft tissue tumour arising from muscle cells. Rhabdomyosarcoma of the extremities is more prevalent in adolescents and is typically of the alveolar type. *Case report*: We report a case of a 7-year-old girl, with an alveolar rhabdomyosarcoma of the left hand. Ultrasound and MRI shows a mass measuring 1.0x1.8x2.4cm at 5th metacarpal bone suggestive of giant cell tumour of tendon and peripheral nerve sheath tumour tendon sheath respectively. Histologically shows nests of polygonal cells separated by fibrovascular septae, some arranged in alveolar pattern. Markedly pleomorphic nuclei with coarse chromatin, small nucleoli and ample clear to eosinophilic cytoplasm. Rhabdomyoblasts with occasional strap cells and high mitosis count are observed. The tumour cells are seen dissecting the adjacent skeletal muscle fibres. The tumour cells are strong and diffusely positive for desmin, myogenin and Myo D1. *Discussion*: Alveolar rhabdomyosarcoma with strong and diffuse positivity for Myogenin as compared with embryonal type that shows patchy positivity. The genetic testing shows FOXO1 rearrangement, either t(1; 13) (PAX3-FOXO1) or t(2; 13) (PAX7-FOXO1). This entity's resemblance to other small round, blue-cell tumours such as lymphoma, small cell osteosarcoma, mesenchymal chondrosarcoma and Ewing sarcoma, hence rhabdomyosarcoma can be challenging to pathologically identify. It is highly aggressive and rapidly growing with lymphatic and haematogenous spread, hence early diagnosis and treatment may improve prognosis. Immunohistochemical, molecular genetics, and/or ultra-structural methods may be required to confirm the diagnosis of rhabdomyosarcoma.

AP2: Hepatocellular carcinoma lymphocyte rich variant, a rare subtype of hepatocellular carcinoma

Nor Akmar Sulaiman[1], Nur Aini Abu Bakar[1], Maizaton Atmadini Abdullah[2], Fauzah Abdul Ghani[2]
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Introduction: The lymphocyte-rich variant of hepatocellular carcinoma (HCC) accounts for 1% of all HCCs and is characterized by extensive intratumoural lymphocytic infiltration. It has been called lymphoepithelioma-like HCCs and exhibits lymphoid aggregates or follicles within the tumour. *Case report*: We describe a case of a 66-year-old Malay lady, with underlying hypertension and pemphigus vulgaris, incidental findings noted transaminitis with very high alpha-fetoprotein. CT scan of the liver shows a huge caudate lobe and segment 7 lesion, likely representing hepatocellular carcinoma. Thus, liver lobectomy was performed. Grossly show well-circumscribed solid yellowish to tan cut mass measuring 97mm in widest diameter. Histologically shows circumscribed nodule composed of malignant hepatocytes arranged predominantly in small acinar and vague lobules separated by thin fibrous septal. Marked lymphocytes infiltrate present in between the malignant hepatocytes with the formation of lymphoid follicles and occasional germinal centre. The malignant cells exhibit mild to moderate pleomorphism with eosinophilic granular cytoplasm, and centrally located round nuclei with prominent nucleoli. The malignant cells are strongly positive to Heppar-1. *Discussion*: This subtype is male predominance with a mean age of 58 years. Serum AFP is increased in the majority of cases. Marked lymphocytes infiltrate in comparison with conventional HCC. Amplification of oncogenes (CCND1, FGF19, and FGF4) from chromosome 11q13.3 is observed in this subtype. This is associated with increased immune cell infiltration and checkpoint gene expression. Thus, it is more responsive to immunotherapies with a better prognosis in comparison to classic HCC.

AP3: Poorly differentiated neuroendocrine urothelial carcinoma with sarcomatoid differentiation: A rare entity

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Introduction: Poorly differentiated neuroendocrine urothelial carcinoma (PD-NEUC) is a rare entity composed of both poorly differentiated and neuroendocrine features. This subtype is usually detected at an advanced stage with median overall survival of less than one year. *Case report*: We report a case of 83 years old, Malay gentleman with underlying hypertension, ischaemic heart disease and gout presented with painful haematuria. CT urogram and cystoscopy revealed a huge broad based papillomatous tumour at the right posterolateral wall with obliteration of the right ureteric orifice. Microscopic findings show multiple fragments of bladder tissue infiltrated by poorly differentiated malignant cells arranged in solid sheets and clusters, infiltrating into the muscularis propria. Some have rosettes formation arrangements. The tumour cells showed 40% neuroendocrine, 15% sarcomatoid differentiation and 5% conventional urothelial carcinoma. Mitoses are abundant with 40% tumour necrosis. Malignant cells are positive for all neuroendocrine markers. The sarcomatoid component was positive for Vimentin and focal positivity for P63. Ki67 was 70-80%. *Discussion:* The diagnosis of PD-NEUC may be challenging as it may mimic other types of urothelial carcinoma. PD-NEUC differs from other types of UC by its high proliferation rate and high mitotic index, as well as by the frequent presence of mutations that are different and unique from those seen in other types of UC. PD-NEUC is a rare and aggressive subtype of urothelial carcinoma typified by the presence of poorly differentiated and neuroendocrine characteristics. PD-NEUC is difficult to treat due to its aggressive nature and limited efficacy in the treatment.

AP4: Syncytial nuclear aggregates in gestational diabetes mellitus

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Introduction: Syncytial nuclear aggregates (SNAs), clusters of syncytiotrophoblasts' nuclei of human placenta, are increased in advanced gestation and in some pregnancy pathologies such as gestational hypertension and pre-eclampsia. Although the formation of SNAs is poorly understood, oxidative damage and placental malperfusion are believed to play an essential role in the mechanism. The aim of our study is to determine if SNAs are increased in gestational diabetes mellitus (GDM) compared with the control group. *Materials & Methods:* A total of 54 cases of GDM placentas and 33 cases of gestational age-matched control were recruited. The respective slides were retrieved and reviewed. Five x100 power fields were randomly selected and the total numbers of SNAs per villous were counted. Clinicopathological data such as gestational age, maternal age, placental weight and fetal outcomes were collected. *Results:* Across all gestational age, GDM placentas did not show significant increase in SNAs formation compared with the control group. Nonetheless, we observed a significant raise in SNAs per villous (54.3%) in near-term GDM placentas when compared with the control group (37.2%) (p=0.01). Birth weight, placental weight, maternal age and gestational age did not increase the risk of SNAs formation in GDM placentas. *Discussion:* Our findings emphasized the importance of glycaemic control, which may help to prevent the increase in SNAs formation, an indicator of placental malperfusion.

AP5: Epstein-barr virus-associated smooth muscle tumours in HIV-positive patient

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Introduction: Epstein-Barr virus (EBV)-associated smooth muscle tumour is a rare smooth muscle neoplasm that has recently been increasingly recognized in immunocompromised patients. *Case Report:* A 51-year-old male with underlying HIV infection presented with vision impairment. CECT brain and neck showed right tonsillar mass with left level V enlarged lymph node with extraaxial dural and cerebellar lesion. He underwent tonsillectomy and subsequently craniotomy for excision of tumour.

Discussion: Microscopically, the tumours from right tonsil and brain were composed of round to oval epithelioid cells and occasional spindle-shaped cells arranged predominantly in sheets. The neoplastic cells exhibited mild pleomorphism, having open nuclear chromatin with prominent nucleoli and moderate amount of eosinophilic cytoplasm. These tumour cells were immunoreactive to smooth muscle actin, Vimentin and EBV-encoded RNA (EBER) in situ hybridization. EBV-associated smooth muscle tumour is very rare in the head and neck region. Nonetheless, it has a predilection to occur in the sites that are unusual for conventional smooth muscle tumours. The diagnosis of EBV-associated smooth muscle tumour should be considered in the differential diagnoses of a mesenchymal tumour in immunocompromised patients.

AP7: Quantitative interpretation of tumour infiltrating lymphocytes (TILs) of triple negative breast cancer

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Introduction: The potential of TILs as prognostic markers in TNBC has been recognised. However, the guideline developed by the Immune-Oncology Biomarker Working Group (TIL-WG) relies on a subjective method resulting in low precision. To address these limitations, the TIL-WG recommends using computational algorithms adhering to their guidelines for an automated TILs assessment model. However, the training and validation of such a model still requires manual ground truth annotations. To address this gap, this study aims to create a digital dataset of whole slide images (WSI) for TNBC of H&E and IHC-stained slides. *Materials & Methods*: A total of 46 TNBC cases was selected and stained with H&E and IHC stains. The slides were then scanned at 20x magnification. Two pathologists independently reviewed the slides following the TIL-WG guidelines, assessing the percentage of sTILs and iTILs per mm2 of the tissue. The interrater reliability was assessed using the intraclass correlation coefficient (ICC) and Cohen's kappa (κ). A third pathologist reviewed cases with poor agreement, and contributing pathologic features were examined. *Results:* The results showed good consistency (ICC = 0.79) and moderate agreement (ICC = 0.65) for sTILs evaluation, while moderate reliability was observed for iTILs evaluation (ICC consistency = 0.70, ICC agreement = 0.61). Cohen's kappa analysis demonstrated fair agreement for both sTILs and iTILs in manual TILs assessment. *Conclusion:* This study has developed a digital dataset of TNBC H&E and IHC stained slides with manual pathologist-derived scores. This dataset serves as a valuable resource for developing computational algorithms that can accurately evaluate TILs in TNBC.

AP8: Association between dietary behaviours and weight changes among UNIMAS pre-clinical medical students during Covid-19 period

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Introduction: Movement Control Order (MCO) during COVID-19 pandemic period was believed to influence the routine lifestyle among Malaysians due to confinement of individuals to their home. This study was conducted to investigate the changes of lifestyles and body weight status among university students and the factors that associated with the changes in Kuching, Sarawak. *Materials and Methods:* This cross-sectional study involved 214 university students through convenient sampling. Data collection was conducted by using a structured questionnaire that was disseminated via google form. Information on the sociodemographic profiles, dietary behaviours (eating of leftover food, water drank per day, and meal skipping), weight changes, and self-reported weight and height were collected. The chi-square test of independence was used during data analysis. *Result:* The study revealed that 35% of respondents perceived themselves as "increase a lot of weight" and 39.3% of the respondents declared skipping one or more of the main meals. The weight change was associated with race (p=0.012), change in number of daily meals (p=0.003), body weight status (p<0.001) and eating habits during COVID-19 pandemic(p=0.002). *Discussion:* Regular health promotion in university campus is needed to increase awareness among the university students about the importance of healthy eating.

AP9: Lymphangiomatous polyp arising from the tonsil

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Introduction: Lymphangiomatous polyp of the tonsil is a benign tumour. Its differential diagnosis includes fibroepithelial polyp, squamous papilloma, angiofibroma, haemangioma, arteriovenous malformation, hamartoma and lymphangioma. *Case report:* A 33-year-old man presented with 2 months history of feeling of foreign body sensation in the throat. He had a history of recurrent tonsillitis of about 2 to 4 times each year. There was neither pain nor itchiness. There was no significant past medical or surgical history. Examination revealed a nodular red coloured polyp on the left tonsil. Intraoperatively, both tonsils were enlarged with a polyp at the inferior pole of the left tonsil. Bilateral tonsillectomy was performed. Examinations of the oral cavity, nasopharynx, and larynx were normal. Histopathological examination showed a polyp arising from the surface of the tonsil. The polyp was soft, light brown and had a smooth surface. It measured 1.0 x 0.8 x 0.5 cm. Histologically, it was covered by squamous epithelium and is composed of numerous vascular channels containing lymphocytes and eosinophilic material, in a fibrous stroma. Immunohistochemically, the endothelial cells were positive toward CD31 and D2-40. At one week follow up, patient was well with no bleeding. *Discussion:* The characteristic histological features of a lymphangiomatous polyp are benign vascular proliferation with variable fibrous, adipose and lymphoid stromal components. Nested intraepithelial

epidermotropism of lymphocytes can be observed. The vascular channels are typically thin-walled and contain eosinophilic proteinaceous material and lymphocytes. There was no incidence of recurrent or malignant transformation.

AP10: Pathology of myxoma: A rare benign breast tumour

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Introduction: Myxoma is an uncommonly encountered benign mesenchymal tumour of the breast. It can occur as a component of autosomal dominant Carney complex, which are commonly multiple and bilateral. *Case report:* A 41-year-old lady presented with gradually enlarging, painless right breast mass for four months. Mammographic examination showed two suspicious well-defined high-density lesions at the upper mid-quadrant of right breast. Ultrasound of the right breast further delineate an ill-defined heterogenous hypoechoic lesion at right breast measuring 3.2 cm in largest dimension with minimal internal vascularity and no clear fat plane with the underlying pectoralis muscle. Another smaller mass measuring 2.8 cm is present adjacent to the main breast lesion. A biopsy of the mass was performed and was reported as benign fibroepithelial lesion. With a clinical impression of phyllodes tumour, she underwent a wide local excision of the right breast lump. Intra-operatively, two mucinous-like lesions are noted within the right breast. Nevertheless, the final histopathological examination was reported as myxoma. *Discussion:* A newly discovered breast lesion in a woman over 40-year-old is suspicious and warrant further investigations to exclude malignancy. Albeit rare, myxoma of the breast should be considered as a differential diagnosis of mucinous-like breast mass.

AP11: Cervical small cell neuroendocrine carcinoma: A case report

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Introduction: Cervical cancer is the second commonest cancer among reproductive aged women in Malaysia. Cervical neuroendocrine cancers (CNECC) accounts for <2% of all cervical malignancies. Due to its rare incidence, limited data available to study its clinical presentation, histopathological characteristics and clinical outcomes. *Case report:* We present a case of a 37 years old lady with a previous history of subfertility of 14 years. She presented with a 3-months history of per vaginal bleeding and found to have cervical mass. Histopathological examination of the cervical tissues showed small cell neuroendocrine carcinoma (SCNEC). She refused for total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) but agreed for chemotherapy of which she defaulted after 3 cycles and later became pregnant. Subsequently, she delivered a baby via emergency Ceasarean section for foetal distress. Intra-operatively, there were ruptured left ovarian tumour that showed SCNEC morphology. A tumour with similar morphology also seen at the lower uterine segment. At 7 weeks post-delivery, she developed generalised tonic-clonic seizures. Repeated imaging studies showed brain metastasis. Patient and family did not consent for further treatment and she eventually succumbed to death a short time later. *Discussion:* Due to its clinical presentation might be similar to any other cervical tumour cases, CNECC should be invariably considered as differentials. Histopathological study plays a pivotal role to rule out any mimicker; which might have different characteristics of metastatic potential and therapeutic options; that could masquerade the disease particularly in advanced stages.

AP12: Dowling Degos disease: A rare genodermatosis

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Introduction: Dowling Degos disease (DDD) is a rare inherited genodermatosis in which there are spotted and reticulate pigment macules of the flexure. Onset is typically after puberty and commonly occurs in the third to fourth decade of life and is slowly progressive. There are less than 50 cases reported in the literature. We present a case of Dowling Degos disease diagnosed in our institution. *Case report:* This is a 55 years old male with underlying hepatitis C and hypertension. He presented with asymptomatic hyperpigmented macules and some papules over the back of his neck for the past 3 years. The clinical diagnosis was Ashy Dermatoses. His mother and uncles from the maternal side have similar skin conditions. Skin biopsy was taken and histopathological examination showed epidermis with filiform down-growth (antler-like pattern) with thinning of the suprapapillary plates and increased pigmentation of the basal layer with occasional dilated pilosebaceous follicles. *Discussion*: DDD is an autosomal dominant reticulate hyperpigmentation disorder, which afflicts only a small number in the worldwide population and is usually recalcitrant to treatment. The differential diagnosis for reticulate hyperpigmented lesions includes Dyschromatosis Symmetrica Hereditaria (DSH), Dyschromatosis Universalis Hereditaria (DUH), and Reticulate Acropigmentation of Kitamura (RAPK). They share similar clinical features, yet they have different pathology findings. The genetic defect of DDD has not yet been well defined and remains inconclusive. Dowling Degos disease can be confused with other entities on the basis of clinical appearance alone, hence a histopathology examination is important to establish the diagnosis.

AP13: CD47 expression in chorioamnionitis

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Introduction: Chorioamnionitis is the inflammation of the placental membrane with presence of neutrophilic infiltration. Currently, the mediators involved in neutrophil recruitment and migration is still under investigation. Early research has hypothesised that CD47 is involved in transmigration of neutrophils across epithelial and endothelial cells. Our objective is to examine the potential involvement of CD47 in neutrophils recruitment and migration in the placenta of patients. *Materials & Methods*: A retrospective study was conducted involving 100 cases with histological diagnosis of acute chorioamnionitis (n=20), subchorionitis (n=20), necrotising chorioamnionitis (n=20) and normal placenta (n=40) over a period of 4 years. Immunohistochemistry was done on the placenta, umbilical cord and placental membrane section. The presence of positive staining and its' intensity on these tissue sections were analysed. *Results*: CD47 positive staining was observed in syncytiotrophoblast, cytotrophoblast, and foetal vessels. A small number of cases also showed positive staining in the maternal vessel, and decidua. All of the stainings were not significantly correlated with chorioamnionitis and foetal inflammatory response syndrome (P>0.05). *Discussion*: Further experiment with a larger sample size and molecular techniques should be conducted in order to corroborate the result.

AP14: Histopathological profile of cervical biopsies in Sarawak

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Introduction: Cervical cancer is the third most prevalent cancer in women in Malaysia. Managing the disease has placed a significant economic burden of approximately RM312 million on the government each year. This study aimed to evaluate the pattern of the histopathological profile of cervical biopsies and to determine the association of risk factors with the findings of the cervical biopsies performed at Klinik Sakit Puan & Infertiliti Universiti Malaysia Sarawak (UNIMAS). *Materials & Methods:* This retrospective study was conducted in a specialist clinic in UNIMAS from January - August 2023. Data regarding the patients and the cervical biopsy findings were recorded using a pre-designed form and were analysed using Statistical Package for Social Sciences version 28.0. *Results:* The most common finding observed was chronic cervicitis (20.9%), whereas cervical intraepithelial neoplasia (CIN) lesions were observed in 20.4% of cases. Among the CIN findings, 87.23% were classified as CIN I, while CIN II and CIN III accounted for 8.51% and 4.26%, respectively. Additionally, 6.38% of the overall CIN findings were associated with HPV. However, there was no significant association between the patient's age and the cervical biopsy finding (p>0.05). *Discussion:* Our study did not observe any significant association between age or ethnicity and the cervical biopsy finding. This study highlights the importance of other sociodemographic data regarding cervical cancer, which should be obtained from all patients referred for a cervical biopsy, as this information is relevant to most healthcare interventions in terms of improving the morbidity and mortality associated with cervical cancer.

AP15: A rare variant of oncocytic mucoepidermoid carcinoma of the parotid gland: A case report

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Introduction: Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy across all ages. This malignancy consists of a combination of squamoid, intermediate cells and mucocytes. A rare variant composed predominantly of oncocytes can be confused with benign entities. We present a case with such an associated lesion. *Case report*: A 61 years old Indian female presented with 10-year history of right preauricular swelling, with recent increase in size and pain for the past year. Cytomorphological examinations of this soft tumour yielded cystic content with no definitive diagnosis. Meanwhile, biopsy revealed a malignant tumour composed of predominantly oncocytic cells, with mucocytes exhibiting intracytoplasmic mucin evidenced by positive Mucicarmine stain and PAS-D resistance. Immunohistochemical markers p63, p40 and CK 5/6 were demonstrable within the basal layer of the intermediate cells. Tumour necrosis and mitosis were scarce with focal perineural invasion observed. *Discussion*: The diagnosis of OMEC is particularly challenging in cytological examinations since it requires at least > 50% population of oncocytic cells, where oncocytic metaplasia is also common in MEC. This variant, even though rare, still has a favourable prognosis. However, the actual challenge in diagnosis lies in differentiating this malignancy with several benign oncocytic lesions that are much more common such as, Warthin's tumour, oncocytoma, and pleomorphic adenoma with oncocytic and mucocytic metaplasia. Ancillary tools like immunohistochemical markers, special stains and molecular studies for MAML2 gene translocation are vital with aiding the diagnosis. Adequate sampling, high index of suspicion coupled with ancillary techniques are crucial to prevent misdiagnosis.

AP16: Impaired DNA mismatch repair and PD-L1 expression in triple negative breast cancers

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Introduction Effects of immune checkpoint inhibitors in triple negative breast cancers have been extensively studied. Clinical trials for triple negative breast cancers have shown clinical improvement using anti PD-L1 antibody in combination with a chemotherapy agent. Solid tumours with impaired DNA mismatch repair (MMR) system (MLH1, PMS2, MSH2, and MSH6

molecules from which phenotype microsatellite instability (MSI) was determined) have shown to respond well to immune checkpoint inhibitor therapy. This study aims to determine the status of MMR and PD-L1 expression in triple negative breast cancers and the role of MMR as predictive immunotherapy biomarker. *Materials and methods*: A total of 47 cases were analysed by performing MLH1, PMS2, MSH2, and MSH6 with PD-L1 immunohistochemistry using clone SP142. The scoring algorithm for PDL-1 was used where the cases are positive if more than 1% of immune cells were immunoreactive and negative if less than 1% of immune cells were stained. Defective MMR was considered when any of the four MMR proteins show absent nuclear staining. *Results:* PD-L1 positive was present in 20/47 cases (43%) and all samples were positive for MMR except 7 cases (15%) which showed defective MMR protein. In the cases with defective MMR protein, only a single protein expression is lost. *Discussion:* Preliminary descriptive analysis showed inconsistencies between PD-L1 positivity and MMR expression status. Further studies with a larger cohort are warranted to explore the significance of defective MMR protein as a predictive biomarker for immunotherapy in triple negative breast cancers.

AP17: Steroid cell tumour of ovary - rare case series

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Introduction: Steroid cell tumours (SCT) are very rare ovarian malignancies under sex-cord-stromal tumours (pure stromal tumours) of the ovary. Most cases fall into the 'not-otherwise-specified' (NOS)-category and the rest are malignant SCT. The mean age of patients is 43 years old and frequently presented with endocrine symptoms (virilisation, hirsutism, etc.). Here, we report 2 cases of SCT with different presentations in our centre over the last 5 years. *Case series:* Case 1: A 69-year-old post-menopausal lady presented with virilisation with increased serum cortisol and testosterone levels. Scan showed a left ovarian solid-cystic mass measuring 8.5cm. Case 2: A 65-year-old post-menopausal lady presented with loss of weight but no endocrine symptoms with normal hormone levels. Scan showed a right ovarian solid mass measuring 7 cm. *Discussion:* Microscopically, both tumours composed of sheets-and-lobules of neoplastic cells exhibiting round vesicular nuclei, conspicuous single central nucleoli and abundant clear-to-eosinophilic cytoplasm. No increased mitosis or necrosis. No capsular, lymphovascular or perineural invasion. They are immunoreactive towards sex cord-stromal markers such as Calretinin and Melan-A. Steroid cell tumour usually occurs in child-bearing age group. However, these two cases are odd as they occurred in post-menopausal women. The tumour may present with various presentations including classical symptoms (virilisation and hyperandrogenism), mass with pressure symptoms or asymptomatic. Some literatures associated this tumour with molecular abnormalities such as *B*-catenin activation and stimulatory G-protein mutations that responsible for hormone secretion hence resulting in its paraneoplastic endocrine signs and symptoms. It is usually treated by total abdominal hysterectomy and salpingo-oophorectomy and/or followed by chemotherapy.

AP19: A case of spindle cell squamous carcinoma in post-radiation nasopharyngeal carcinoma

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Introduction: Spindle cell squamous carcinoma is a rare, mucosa-based squamous cell carcinoma with malignant spindle cell component showing propensity for head and neck region. *Case report:* A 72-year-old female with history of nasopharyngeal carcinoma, diagnosed in 1994 and treated with radiotherapy. Currently, she presented with left eye blurring of vision, altered right facial sensation for 2 months and blindness for 2 days. MRI brain showed a locally aggressive sphenoid sinus avidly enhancing soft tissue mass, with left intraorbital extension. Microscopically, biopsies taken from sphenoid floor, sinus and nose showed malignant squamous epithelial cells composed of pleomorphic, polygonal cells exhibiting hyperchromatic to vesicular nuclei with prominent nucleoli and eosinophilic cytoplasm arranged in irregular clusters and trabeculae. In areas, intermingling spindle shaped cells arranged in storiform pattern are observed. The polygonal cells were immunoreactive to cytokeratin 5/6, EMA, p63 and the spindle cells showed heterogenous positivity to p63 and SMA. Desmin, CD34, LCA and EBV-encoded RNA (EBER) in situ hybridization are negative. *Discussion*: Spindle cell squamous carcinoma is an aggressive variant of squamous cell carcinoma that may mimic sarcomas, other spindle cell malignancies and some benign entities like granulation tissue with reactive stromal changes particularly after radiotherapy. Tumours with a conventional squamous cell carcinoma component appear to have a better prognosis while radiotherapy-induced tumours have a worse prognosis than those arising de novo.

AP22: Upregulation of connexin 40 in the endothelial cells of placenta with acute chorioamnionitis

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Introduction: Connexins 43 (Cx43) and Connexins 40 (Cx40) were known to be involved in leukocytes recruitment in endothelial cells during acute inflammation, evidenced by upregulation of endothelial Cx43 or up-/downregulation of endothelial Cx40. They were also found in placenta and participated in placental development, and therefore might play a role in acute chorioamnionitis (ACA). Our study aimed to characterise the expression of Cx43 and Cx40 in the different cell types of placenta, and to correlate their expression with the severity of chorioamnionitis and their association with adverse perinatal outcomes. *Materials & Methods:* This was a cross sectional study on 81 archived placenta samples, consisting of 39 ACA placentas and 42 non-ACA placentas. All placenta samples were stained using anti-Cx43 and anti-Cx40 antibodies. The expressions were evaluated on the various cell types in the placenta. *Results:* Mothers with ACA were more likely to be primigravida (p<0.001), and a higher stage of foetal inflammatory response was more likely to be associated with neonates

with lung complications (p=0.041). Significant upregulation of Cx40 expression in stem and maternal vessels' endothelial cells were observed in ACA, compared to non-ACA (p<0.001 and p=0.037 respectively). While the Cx43 expressions were not expressed in most of the cell types in ACA. Both Cx43 and Cx40 were not associated with adverse perinatal outcomes. *Discussion:* Cx40 was upregulated in ACA and may play a role in the pathogenesis of ACA. Further study on Cx40 in ACA may shed light to its role in the development of inflammation in placenta.

AP23: Electron microscopy of formalin fixed (wet specimen) and paraffin embedded specimen: A tertiary centre experience

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Introduction: Transmission Electron Microscopy (TEM) is a useful tool to examine detailed ultrastructures of tissues and cells, widely utilised in renal and cardiac biopsies. However, a known constraint of TEM is the emphasis on receiving fresh tissue, thereby excluding examination for cases that had already been fixed in formalin or embedded in paraffin. Here, we present two such cases which had successfully been processed and evaluated using TEM: a biopsy of heart tissue which had been fixed with formalin (wet specimen) and a renal biopsy which had been embedded in paraffin block. *Materials & Methods:* Formalin-fixed heart tissue: Specimen was rinsed in distilled water and then fixed in glutaraldehyde overnight. Paraffin block renal tissue: The selected area is cut out from the block, and was processed in xylene and alcohol. Both specimens were then processed the same way as tissue fixed with glutaraldehyde. *Results:* For both the formalin fixed and the paraffin embedded specimens, there were slight difference in certain ultrastructures. However, the final interpretation and diagnosis do not differ significantly compared to fresh tissue fixed in glutaraldehyde. *Discussion:* These techniques show that formalin fixed tissue and paraffin embedded tissue can provide reliable findings on electron microscopy, therefore reducing the need for repeated biopsy to retrieve fresh specimen.

2. Chemical Pathology

CP1: A Rare Case of MELAS Syndrome

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Introduction: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare mitochondrial disorder that is present in childhood and is inherited maternally. The rarity and complexity of its manifestations can make it challenging to diagnose, often requiring a high index of suspicion. *Case report:* A 7-year-old boy presented with recurrent jerky movements in his right upper and lower limbs, uprolling eyeballs, and post-ictal vomiting. No recent trauma or family history of epilepsy was reported. Brain magnetic resonance imaging (MRI) showed evidence of cerebritis and basal ganglia calcification, initially leading to treatment for meningoencephalitis. However, the patient's unexplained developmental delay, episodes of encephalopathy, muscle cramps, and easy fatigability suggested a mitochondrial disease. Genetic testing revealed a heteroplasmic pathogenic variant in the MT-TL1 gene consistent with MELAS syndrome. *Discussion:* MELAS is a rare neurodegenerative disorder with maternally inherited, polygenic mutations in mitochondrial DNA. The underlying mechanism of MELAS is not completely understood but may involve impaired mitochondrial energy production, microvasculature angiopathy, and nitric oxide deficiency. In addition to neurological symptoms and lactic acidosis, MELAS may affect other organ systems, such as cardiac arrhythmia, as well as causing diabetes and chronic fatigue. While the presentation of MELAS can vary, most patients experience encephalopathy, myopathy, and stroke-like episodes. Diagnosing MELAS can be challenging, as it can be misdiagnosed as other conditions such as cerebral infarction, encephalitis or even myasthenia gravis. The diagnosis can be narrowed by MRI scan, muscle biopsy, and finally, be confirmed with genetic analysis.

CP2: A Report of Dual Bands in Relapsed IgG Lambda Myeloma: Truth or Lie?

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Introduction: Relapsed/refractory multiple myeloma (RRMM) occurs when a patient is non-responsive to treatment, disease is progressive despite therapy, or disease has worsened within 60 days of the last treatment in a patient who had achieved a minimal response or better on prior therapy. Daratumumab has been approved as the first-line medication for RRMM. However, this anti-CD38 mimicking M-protein poses a challenge in interpreting electrophoresis and immunofixation. *Case report*: A 72-year-old woman was diagnosed with multiple myeloma Stage 3A after presenting with chronic lower back pain. Initial laboratory investigations showed hypochromic microcytic anaemia with marked rouleaux, normocalcaemia, estimated-glomerular filtration rate of 45 ml/min/1.73m^2, IgG lambda paraproteinaemia with a concentration of 30.5 g/L and immunoparesis, and 16% plasma cells on bone marrow aspiration. Velcade, thalidomide, and dexamethasone were initiated but the patient developed peripheral neuropathy. Thalidomide was withdrawn, and stringent complete remission was achieved, confirmed by serum-free light chain. Complete remission was seen on serum and protein electrophoresis (SPE) with velcade and dexamethasone. Biochemical relapse was observed after three months of velcade maintenance. Daratumumab

was initiated, and a repeat SPE after the second cycle of daratumumab showed an additional new band distal to the initial M-protein. *Discussion*: Multiple ways to mitigate daratumumab interference have been explored and proposed. Nonetheless, the use of daratumumab in practice is not extensive and reserved mainly for RRMM. Moreover, low-resource laboratories in Malaysia will still encounter challenges in terms of operating costs. In conclusion, good laboratory practice can outwit the various steps in dealing with daratumumab interference.

CP3: Hyponatraemia followed by Hypernatraemia in a case of Tuberculous Meningoencephalitis

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Introduction: Tuberculous meningoencephalitis is a rare presentation of extrapulmonary tuberculosis. Hyponatraemia followed by hypernatraemia is an unusual manifestation of this disease. *Case report:* Here, we present a case of tuberculous meningoencephalitis complicated with sodium imbalance in a former intravenous drug user. His laboratory investigations upon admission showed hyponatraemia, decreased serum osmolality, inappropriately concentrated urine, normal renal and adrenal function indicating syndrome of inappropriate antidiuresis (SIAD), which is commonly associated with tuberculous meningitis. Instead of fluid restriction, he was treated with intravenous fluid therapy in an effort to replenish the electrolytes that were lost. Unfortunately, his brain pathology worsened. An increasing trend in urine output and sodium concentration suggested central diabetes insipidus (CDI), which is an uncommon complication of tuberculous meningitis. Despite intervention with desmopressin on day 6 of admission, he passed away on the same day due to haemodynamic instability. *Discussion:* Extrapulmonary tuberculosis is not a common disease, not to mention its complications. Understanding the underlying aetiology of hyponatraemia has significant implications for fluid management. This case highlights the importance of being attentive to a patient's clinical status and recognising associated complications to ensure prompt, appropriate treatment is administered without jeopardising the patient's outcome.

CP4: Comparison of serum and plasma samples for measurement of biochemistry tests

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Introduction: Although the utility of plain vacutainers (SST) for biochemistry tests offers a degree of standardisation in many laboratories, heparinised vacutainers is preferred by others owing to their shorter processing time; whilst the use of both types are practised in some laboratories. Results of many biochemistry tests from both sample types have been considered equivalent. This study aimed to compare results from plasma and serum samples for eleven biochemistry analytes. *Materials and Methods:* Serum and heparinised samples were collected from twenty participants during a single venipuncture. Sodium, potassium, chloride, urea, creatinine, albumin, ALT, calcium, magnesium, CRP and LDH were analysed on Beckman Coulter DxC 700 AU analyser. Percentage or absolute difference between serum and plasma values more than Analytical Performance Specification was considered clinically significant. Data were evaluated by Student's paired t-test or Wilcoxon signed rank test and $p<0.05$ were considered statistically significant. *Results:* Percentage differences of result between serum and plasma samples for all analytes ranged from 0% to 13%. There were statistically significant differences of test values between serum and plasma for analytes chloride, urea, creatinine and ALT but clinically insignificance. Two analytes, namely potassium (+7.3%) and LDH (+11.4%) were clinically significant differences (exceeded the RCPA recommended Analytical Performance Specification) and reached statistical significance ($p<0.05$). *Discussion:* Significant differences that may affect clinical decision- making were seen in certain analytes yielded from serum and plasma samples, including those considered equivalent by the manufacturer. It is vital to maintain the same type of sample throughout patient monitoring. Ideally, one should verify the manufacturer's claim. Unless evidenced, interchangeable use of both types of samples should not be practiced.

CP5: Severe hyperammonaemia in a newborn

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Introduction: Severe hyperammonaemia is a life-threatening condition, which if left untreated, rapidly leads to encephalopathy, cerebral oedema and death. The underlying cause can be due to inherited or acquired disorders. We report a case of ornithine transcarbamylase (OTC) deficiency in a newborn presenting with severe hyperammonaemia. *Case report:* A baby boy, born full-term with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, was intubated at 30 minutes of life for transient tachypnoea of the newborn (TTN). He managed to be extubated at 21-hour and formula feeding commenced soon after. 41 hours later, he developed several episodes of seizures associated with generalised hypotonia and respiratory distress. Immediate investigations showed a plasma ammonia of 2796 (18-72 umol/L) which worsened to 4183 umol/L on a repeat sample. Other abnormal findings include respiratory alkalosis, hypocalcaemia, increased lactate and deranged coagulation profiles. Plasma amino acid analysis showed raised glutamine and alanine with undetectable citrulline, whilst urine organic acid showed a significant increase in orotic acid consistent with OTC deficiency. He progressively deteriorated, developed cerebral oedema, and succumbed to death at 91 hours of life. *Discussion:* OTC deficiency is a rare X-linked genetic disorder characterised by a complete or partial lack of the OTC enzyme, resulting in excessive accumulation of ammonia. Clinical presentations vary depending on the degree of enzyme deficiency. In the neonatal onset, the symptoms often start between 24 hours to a few days after birth, following protein feeding. Early identification and management are crucial to prevent neurodevelopmental complications.

CP6: Laboratory approach to pseudohyperkalaeamia: A case of chronic lymphocytic leukaemia (CLL)

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Introduction: Pseudohyperkalaemia is a false elevation of potassium concentration and may complicate the identification of true hyperkalaemia. Failure to distinguish between these two conditions may result in unnecessary potassium correction leading to life-threatening hypokalaemia. *Case report:* We report a case of undiagnosed pseudohyperkalaemia in a newly diagnosed chronic lymphocytic leukaemia (CLL) patient. She presented to the hospital with an infected scald wound. During investigations, she was incidentally found to have hyperleukocytosis and an extremely elevated plasma potassium concentration. She received multiple potassium correction treatments although there was no clinical evidence of hyperkalaemia. Despite treatment, her potassium concentration remained high. Laboratory personnel were alerted, and her case was reviewed. The haemolysis index was negative in most of her samples. Potassium concentrations were markedly elevated in both plasma and serum samples with plasma samples were reported higher than serum samples. EDTA contamination was excluded, and analytical performance was within the laboratory quality specification. Whole blood potassium was not analysed. It was assumed that the hyperkalaemia in this patient was artificially produced after the diagnosis of CLL was made and potassium correction was discontinued. *Discussion:* It is important to recognise this condition early to avoid imprudent treatment of the patient. As laboratory personnel, it is our utmost responsibility to provide high quality results. Therefore, we would like to propose a stepwise approach to hyperkalaemia for early detection of erroneous results and improve laboratory service.

CP7: False positive serum protein electrophoresis in a patient with multiple myeloma on daratumumab

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Introduction: Daratumumab, a monoclonal antibody (mAb) targeting CD38 is an emerging therapeutic option for patients with relapsed multiple myeloma (MM). Its use however can complicate interpretation of serum protein electrophoresis (SPEP) and immunofixation (IFE). *Case report:* A 58-year-old woman diagnosed with IgA Kappa MM had autologous stem cell transplant performed in November 2020. She relapsed in June 2021 and treated with Bortezomib, Cyclophosphamide, Dexamethasone and Pomalidomide. Unfortunately, her disease progressed within four months. Hence, the regime was changed to Bortezomib, Dexamethasone and Pomalidomide with the addition of Daratumumab. Analysis of SPEP and IFE three months after showed an additional monoclonal band. The first monoclonal band was of IgA Kappa type having a similar electrophoretic position as previous SPEP findings, measuring 14.4 g/L. The additional band was IgG Kappa type migrating to the cathodic end, measuring <0.15 g/L. The additional band was not confirmed by daratumumab-specific immunofixation electrophoresis reflex assay (DIRA). However, due to recent treatment with Daratumumab, plus the low concentration and the location, we think that the band was not attributed by the MM. *Discussion:* SPEP and IFE are unable to distinguish between endogenous monoclonal protein and therapeutic antibodies. False positive SPEP in patients on these treatments may lead to incorrect treatment response assessment. DIRA had been shown to mitigate the interference caused by treatment by daratumumab. Monitoring of residual disease by serum free light chain assay and development of standardised guidelines are also vital to patient care in this era of daratumumab-based therapies.

CP8: A case of osmotic demyelination syndrome in a symptomatic hyponatraemic patient complicated with metabolic encephalopathy

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Introduction: Osmotic demyelination syndrome (ODS) is a clinical syndrome seen following aggressive correction of severe hyponatremia. Chronic alcohol use, malnutrition and electrolyte derangement are additional risk factors promoting demyelination in ODS. *Case report:* A 56-year-old woman with underlying diabetes mellitus, hypertension, chronic hepatitis B carrier and fatty liver was admitted for drug-induced symptomatic hyponatremia. She presented with dizziness, nausea, vomiting and tinnitus for the past 3 days. On further questioning, she was taking topical steroid and acetazolamide for two months after her corrective surgery for right retinal detachment. Clinical examinations were unremarkable. Biochemical profile on the electrolytes and the osmolality showed hypotonic hyponatraemia with severe hyponatraemia and below range serum potassium, phosphate, and magnesium. Serum osmolality and urine osmolality were 222 & 457 mOsm/kg respectively. Urine sodium was 35 mmol/L. Active and simultaneous correction of electrolyte imbalances by isotonic saline led to an overly rapid increase of serum sodium levels (20mmol/h over 48h). The isotonic saline regime was replaced with 5% dextrose infusion. However, Glasgow Coma Scale (GCS) level further dropped and subsequent magnetic resonance imaging (MRI) brain findings were consistent with osmotic demyelination. Steroids were administered intravenously with progressive improvement of biochemical and clinical abnormalities. ***Discussion*:** This report illustrates an unusual case of ODS, occurred after an excessive rate of correction of hypotonic hyponatraemia obtained with isotonic saline infusion. A more cautious and thoughtful correction of electrolyte imbalance, would have probably prevented the onset of ODS in this patient.

CP9: Cost-effectiveness of implementation of aspartate aminotransferase elimination from the liver function test panel

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Introduction: Significant savings on reagent costs has been shown by selectively limiting aspartate aminotransferase (AST) testing from routine liver function test (LFT) panel, without affecting patient's outcome. We have eliminated AST from routine LFT panel offered in our Chemical Pathology laboratory in a state hospital, as of November 9, 2021 as part of a strategy for judicious and cost-effective measures. We conducted a clinical audit to evaluate the cost-effectiveness of eliminating AST from the routine LFT panel and introducing an automatic AST reflex testing in our laboratory. *Material & Methods:* This was a retrospective audit, based on monthly workload for LFT and AST as standalone requests, over a 12-months period, starting from the day of introduction of AST removal from routine LFT panel. The cost per test for AST during this audit was RM0.90 (excluding consumables). Saved costs were calculated based on monthly workloads, extracted from our laboratory information system. *Results:* A total of 75,618 AST tests with a total cost of RM68,056.20 were saved throughout the 12-months period after implementing AST elimination from routine LFT panel. *Discussion:* Eliminating AST from the LFT panel resulted in significant cost-savings over a one year-period. We highlighted the cost-saving measure of eliminating AST from the routine LFT panel as an effective measure to reduce overutilisation of laboratory testing, without compromising patient's safety.

CP10: Correlation of HbA1c value between Variant II Turbo HbA1c analyser and D100 HbA1c analyser among diabetic patients with P3 > 5%

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Introduction: Glycated haemoglobin A1c (HbA1c) assay is most widely used in diabetic patients to assess long-term glycaemic control. A P3 peak > 5% with the presence of a variant window on Variant II Turbo HbA1c analyser is not reportable unlike using D100 HbA1c analyser where it is still reportable. We aimed to determine the correlation and agreement between measured HbA1c values that are not reportable on Variant II Turbo HbA1c with that measured on D100 HbA1c. *Materials & Methods:* Blood samples of 40 diabetic patients from Hospital Tengku Ampuan Rahimah (HTAR), Klang was analysed for HbA1c on Variant II Turbo HbA1c analyser (Chemical Pathology Unit, HTAR, Klang) and D100 HbA1c analyser (Chemical Pathology Unit, Hospital Kuala Lumpur). A Bland-Altman plot and linear regression analysis were used to determine agreement and correlation between both analysers. *Results and Discussion:* The Bland-Altman plot showed dispersion of data within the 95% limit of agreement with positive mean bias of 0.2779%, which is lower than the allowable bias of 4.7%. The linear regression showed r = 0.99 indicating there is a strong correlation between the analysers. The slope (m) exceeded about 0.0647, indicating a 6.47% higher HbA1c result with Variant II Turbo. The intercept (c) was -0.3083 indicating that the absolute difference is 0.3083 lower with Variant II Turbo. *Conclusion:* The strong correlation and good clinical agreement of HbA1c values between both analysers indicate that these analysers can be used interchangeably.

CP11: Value assignment of mean, SD and quality control ranges for technopath Multichem QC on Beckman Coulter DxC700 AU Platform

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Introduction: Laboratory quality control is an essential part of ensuring the accuracy and reliability of results released for patient management. The study purpose is to establish mean and standard deviation (SD) for seven analytes in Technopath Multichem QC products. *Materials & Methods*: The study was done from 1-8 August 2022 at Pathology Department, Hospital Sultan Ismail Petra. Technopath Multichem QC materials were analysed on Beckman Coulter (BC) DxC700 AU analyser for 7 analytes (HDL, UIBC, Ammonia, Total Bilirubin, Direct Bilirubin, CSF Glucose and CSF Total Protein) in duplicates, over 10 separate runs over 10 days. A minimum of 20 data points for each control level was generated and recorded in IAMQC Infinity Data Management software. Data generated was reviewed to ensure coefficient variation (CV) is lower than performance goals. Mean and SD values for each analyte were calculated. Outliers whereby data points exceed 3SD, were removed from statistical calculation. *Results*: CV for HDL range 1.38-1.92% (goal <2.85%), UIBC range 1.37-4.13% (<20.0%), Ammonia range 1.03-5.77% (<20.0%), Total Bilirubin 0.96% (<10.0%), Direct Bilirubin 2.39% (<18.4%), CSF Glucose range 5.39-5.40% (<10.0%) and CSF Total Protein range 1.85-2.05% (<17.75). Mean and SD values for each analyte are tabulated. *Discussion*: The Multichem QC materials on BC DxC system gives acceptable analytical performance across all tests evaluated and the values were within analytical performance specification. These values will be used as a guideline by all laboratories that using the same Multichem QC products with same lot numbers to perform method evaluation and establish their own mean and SD.

CP12: Critical value notification: Opening the Pandora's box

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Introduction: Critical values are significant laboratory results that can threaten a patient's life unless appropriate corrective action is taken promptly. Notification of critical values is the responsibility of laboratory personnel. Ineffective notification can lead to delayed diagnosis and treatment, which can potentially affect patient care and safety. We conducted a clinical audit in a Chemical Pathology laboratory of a hospital in Klang Valley to assess the rate of critical values notification. *Materials & Methods:* Six-month retrospective data from 1st January 2022 to 30th June 2022 for serum sodium and potassium levels were extracted from Laboratory Information System (LIS) and manual documentation. Notification rates were calculated monthly by dividing the total number of critical results notified by the total number of critical results. Notification was considered valid if it was done within 30 minutes after result verification. *Results:* Monthly notification rates for sodium and potassium ranged from 24 to 39.1% and 29.2 to 55.1%, respectively. The cumulative notification rate for both analytes ranged between 28.3 and 44.4%. Documentation of critical value notification for both analytes in LIS was 8.7%, and manual documentation was 29.2%. Several issues were identified during this audit including preferential analyte notification, unstandardised notification documentation, and data discrepancies documented in LIS and manual forms. *Discussion:* Improvement plans include enforcing proper workflow adherence, standardising documentation and improvising LIS by adding a critical value button and pop-up box. Overall, the commitment to critical value notification is still low. Implementation of standardised preventive measures can reduce diagnostic errors and improve patient safety.

CP13: Omentin serum levels in obesity and diabetes

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Introduction: Omentin is a newly identified secretory protein highly and selectively expressed in visceral adipose tissue relative to subcutaneous adipose tissue. Previous studies found inconsistent results on the relationship between type 2 diabetes mellitus (T2DM) and obesity with omentin concentrations. Our study aimed to determine the serum omentin levels in healthy controls and obese individuals with different HbA1c values. Furthermore, to investigate the correlations of omentin with HbA1c in obese patients undergoing metabolic surgery. *Materials & methods:* Subsamples were utilized from obese patients recruited for a multicenter metabolic surgery study. Healthy individuals (BMI between 18.5-22.9 kg/m^2) were recruited as the control group (n=14). Patients aged between 18-65 years; men and women; with BMI≥25kg/m^2 (Asian BMI:WHO/IASO/IOTF,2000); and scheduled for metabolic surgery were included in the study and were grouped into non-diabetes (n=22), prediabetes (n=18), and T2DM (n=17) according to HbA1c values. Clinical information and blood samples were collected, and serum omentin levels were measured using an enzyme-linked immunosorbent assay. *Results:* Significant differences were found between groups comparison; healthy controls =92.9 (±19.1)µL; obese without T2DM=125 (±18.3) µL; obese with preT2DM=272 (±34.6)µL; obese withT2DM=260(±29.6)µL (ANOVA, Kruskal-Wallis post-hoc=p<0.0001). There are positive correlations between omentin with HbA1c, BMI, and visceral fat area (p<0.005). *Discussion:* In this preliminary study, omentin levels are higher in prediabetes & diabetes compared to healthy controls and obese without diabetes. Decreased omentin levels may be an important indicator of diabetes. Omentin levels will be monitored 6 months post-surgery to understand its role in diabetes development or diabetes remission.

CP14: The effect of storage temperature on sample stability in the routine clinical laboratory

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Introduction: 'Add-on' tests are often requested for samples already in the laboratory. The main challenge for add-on testing is storage of specimens. This study was carried out to assess whether the stability of common analytes is affected by storage temperature and to determine their suitability for add-on requests. *Materials & Methods:* Twenty samples were collected in two serum separator tubes. The tubes were placed vertically for 30 minutes at room temperature (RT) prior to centrifugation. Samples were stored in group 1) RT and group 2) 2-8°C. Both groups were analysed immediately at baseline then at 6, 10 and 24 hours. Baseline concentrations in both sets of samples were compared with concentrations measured at subsequent time points following storage temperatures described above. Significant analytical changes were evaluated. *Results:* Potassium, sodium, chloride and amylase showed significant changes in both storage conditions at 24 hours; thus, not suitable for add-on testing if stored longer than that. Alkaline phosphatase (ALP), direct bilirubin and total bilirubin are suitable for add-on testing within 24 hours if kept at 2-8°C. Lactate dehydrogenase (LDH) stored at RT is not suitable for 'add-on' testing after 10 hours. *Discussion:* Temperature may affect the stability of some analytes. The degree of sample evaporation is higher when stored at RT causing an increase in concentration which contributes to significant changes. Amending the standard operating procedure to store samples at 2-8°C instead of at RT may allow for 'add-on' of ALP, direct bilirubin, total bilirubin and LDH when stored up to 24 hours.

CP15: Under-five mortality due to inborn errors of metabolism in Malaysia

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Introduction: A fatal severe enzyme deficiency or a co-factor in a metabolic pathway may result in early childhood mortality. The aim of this study was to review the mortality rate of children less than five years old in Malaysia with a diagnosis of inborn errors of metabolism (IEM). *Materials & Methods:* Secondary data were obtained from Malaysian children aged five years old or less who were diagnosed and died with IEM. 36,467 patients' samples underwent selective screening between January 2015 to December 2021. *Results:* Forty-two cases of under-five mortalities were found. 69% aged one month; 31% aged between one month to three years old. 57% were male. Ethnic distribution: Malays (80%), Sabah and Sarawak (7%), Indian (5%) and Chinese (5%). Fatty acid oxidation disorder contributed the most common diagnoses (50%) compared to organic aciduria (21%), urea cycle defect (19%), and congenital lactic acidosis (10%). The 7-year average mortality rate related to IEM in children < five years old per 10,000 population at risk in Malaysia was 1.6 with a range of 0 to 3.8. *Discussion:* There is a variable mortality rate between states in Malaysia. Apart from traditional values of health beliefs and socioeconomic factors, the availability of genetic services may play a major role in detecting IEM as the cause of death in these children. As expanded newborn screening is shown to prevent early mortality, it is only appropriate for all sectors including public, private and non-governmental organisations to contribute more towards preventive healthcare in children.

CP16: Do we need daily analysis of beta-human choriogonadotropin?

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Introduction: Beta-human choriogonadotropin (β-HCG) analysis is useful for screening, diagnosis and monitoring of many reproductive-related diseases. β-HCG analysis is currently offered on every other day in our laboratory, the Chemical Pathology unit, at the state hospital. However, requests have been made by our clinical colleagues to offer β-HCG analysis daily to assist their clinical management. *Material & Methods:* We conducted a 10-week audit in our Chemical Pathology unit, at the state hospital, to determine the cost-effectiveness of daily β-HCG analysis based on our laboratory workload. *Results:* A total of 521 β-HCG tests were requested during the 10 weeks audit period and none of these requests were made as urgent test requests. 123 tests were for pregnancy of unknown location, 110 were for malignancy cases and the remaining were for ectopic pregnancies, molar pregnancies, miscarriages, and gestational trophoblastic disorders. 265 tests were registered on the analysis day and 256 on non-analysis day. Based on the calculation of reagent and quality control material costs, the total weekly cost for daily and every other day analyses of β-HCG were RM296.60 and RM186.30, respectively. This cost difference can cover approximately 500 additional tests per year. *Discussion:* Testing is considered as not cost-effective if daily analysis is less than 30 tests. Clinically, β-HCG is not a diagnostic marker for molar pregnancies, ectopic or pregnancies of unknown location. We recommend that every other day analysis of β-HCG is still cost-effective without affecting the clinical outcomes.

CP17: Rare among the ultra-rare: Report of the first confirmed case of N-acetylglutamate synthase (NAGS) deficiency in Hospital Tunku Azizah

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Introduction: N-acetylglutamate synthase (NAGS) deficiency is the rarest of the urea cycle disorders that, if left untreated, results in hyperammonaemia and significant morbidity and mortality. *Case Report:* A boy was born at term via caesarean section to non-consanguineous parents with birth weight of 3.1kg and good Apgar scores, following an uneventful pregnancy. He was the second child with a healthy sibling. He presented at 59 hours of life with grunting and respiratory distress requiring ventilatory support. He suffered from hypotonia, poor feeding, lethargy, seizures with progressive encephalopathy and EEG showed a burst suppression pattern. Hyperammonaemia was detected at day 6 of life, and he received acute management including peritoneal dialysis, protein restriction, ammonia scavengers and carbamylglutamate, which successfully treated the hyperammonaemia. *Disucssion:* Initial laboratory investigations showed profound hyperammonaemia (>750 mmol/L), with elevated lactate (6.4 mmol/L) and transient impaired renal profile. Plasma aminoacidogram showed significant raised levels of glutamine, glycine, alanine and lysine with mild increased of glutamate and proline along with undetected citrulline and normal arginine. Similar findings were observed from dried blood spot analysis with marked elevation of alanine, proline and glutamate with low citrulline and low normal arginine. Urinary organic acids showed severe lactic aciduria with the absence of orotate. A proximal urea cycle defect was highly suspected and molecular genetic studies confirmed the diagnosis of NAGS deficiency with the identification of two *compound heterozygous* pathogenic variants in the *NAGS* gene (NM_153006.2) with *c.846dupC* inherited from his father and *c.854_858delins GACGCA* inherited from his mother. Genetic counselling was given. This case illustrates the importance of early detection of neonatal encephalopathy due to hyperammonaemia and the

prompt diagnosis of urea cycle defects with the availability of biochemical genetics testing. This has important implications as appropriate treatment especially with carbamylglutamate in NAGS deficiency can improve outcome and reduce morbidity.

CP18: GM1 gangliosidosis in a presumed carrier of *GLB1* pathogenic variant: A case report

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Introduction: GM1 gangliosidosis is a rare class of lysosomal storage disease (LSD). This autosomal recessive disorder is characterised by a biallelic mutation in the *GLB1* gene resulting in the absence or reduction of β-galactosidase enzyme and subsequent accumulation of GM1 ganglioside in various tissues and organs. *Case report:* A case of a one year and eight months old girl with multiple hospitalisations since 3 months old. She showed dysmorphic features with central hypotonia and global developmental delay. Physical examination revealed hepatosplenomegaly, a Mongolian spot over the anterior abdominal wall and cherry-red spot in both eyes. She was then screened for Inborn Error of Metabolism (IEM). IEM screening revealed normal results. At the age of one year and six months, a radiological examination was performed, which showed features of LSD. A molecular genetic testing revealed a monoallelic pathogenic variant in the *GLB1* gene. An enzyme assay showed deficiency of β-galactosidase activity (1 nmol/ml/hour), which concluded the diagnosis. Unfortunately, she died of severe bronchopneumonia at 1 year and 8 months of age. *Discussion:* GM1 gangliosidosis is a progressive neurodegenerative disorder phenotypically classified into three types with type 3 being the most severe and characterised by early childhood death. Diagnosis is established by detection of biallelic pathogenic variant in *GLB1* by molecular genetic testing or by a significant reduction in β-galactosidase enzyme activity by enzyme assay. Currently, there is no definitive treatment. Low prevalence and lack of awareness may contribute to delayed diagnosis. Therefore, early detection is important for intervention and management.

CP19: Evaluation of clinical, biochemical, molecular characteristics and outcome of patients with cystathionine B-synthase (CBS) deficiency and Cobalamin C (cblC) deficiency in Malaysia

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Introduction: Defect of methionine metabolism (cystathionine B-synthase (CBS) deficiency) and cobalamin metabolism (Cobalamin C (cblC) deficiency) is amongst the commonest causes of inherited Hyperhomocysteinemia. We aim to evaluate the diagnosis, treatment and the clinical outcome of affected patients in Malaysia. *Materials & Methods:* Patients were identified from a selective high-risk screening of 82,904 patients in Institute for Medical Research (IMR) between 2010 until 2020 and underwent follow-up in the Genetic Clinic, Hospital Kuala Lumpur (HKL). Data from the medical records were extracted and analysed. *Results:* 10 patients (CBS deficiency = 4, cblC deficiency = 6) were identified with an average age at diagnosis of 4.6 years old, (1 month to 11 years old). The most common clinical presentation is developmental delay with varying levels of total homocysteine (tHcy), methionine and methylmalonic acid (MMA). The most observed mutations in *CBS* and *MMACHC* genes were c.133 c>T (2/4) and c.609 G>A (4/6) respectively. The treatment given shares the same goal of reducing tHcy. All patients exhibit varying degrees of learning disability. 2 patients (CBS deficiency) had severe myopia. Hyperactive and inattentive behaviour were observed more in cblC deficiency. 2 patients (CBS deficiency) developed thromboembolic events at 11 and 21 years old. *Discussion:* Patients with cblC deficiency were detected at younger age and had better outcome following treatment, whereas patients with CBS deficiency presented at school age and already had complication of disease at diagnosis. Early universal screening of both diseases may improve clinical outcomes.

CP20: Fumarase hydratase deficiency- Early diagnosis for a potentially treatable disease

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Introduction: Fumarate hydratase deficiency (FHD) caused by biallelic alterations of the FH (fumarate hydratase) gene is a rare disorder of the tricarboxylic acid (TCA) cycle, classically characterized by neurologic manifestations, a spectrum of brain abnormalities, and excretion of fumaric acid in the urine. *Case report:* A 6-months-old boy was referred for feeding problems, failure to thrive, hypotonia and seizures. Physical examination revealed profound developmental delay, opisthotonic posturing and dystonia. MRI brain showed prominent bifrontal and interhemispheric CSF spaces and enlarged bilateral lateral ventricles. Initial inherited metabolic screening was performed to exclude Glutaric aciduria. However, dried blood spot acylcarnitine and amino acid by Tandem Mass Spectrometry showed non-significant findings. Subsequent urinary organic acids analysis by Gas Chromatography Mass Spectrometry revealed significant elevation of fumarate and other TCA intermediates with mild elevation of 3-methylglutaconate. Whole exome sequencing (WES) detected likely pathogenic compound heterozygous variants in FH gene which supported the diagnosis of FHD. *Discussion*: FHD has a varied clinical phenotype. The clinical presentation of enlarged brain ventricles with seizures, hypotonia, growth retardation and opisthotonos together with the urine

organic acid findings is suggestive of FHD. This case illustrates the importance of early diagnosis of FHD by non-invasive urine organic acid analysis and diagnosis confirmation with molecular analysis.

CP21: Profiling of sample rejection in a diagnostic laboratory of a tertiary hospital in Kuala Lumpur

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Introduction: Minimising sample rejection rate is one of the quality improvements exercises in a clinical laboratory. The Malaysian Society for Quality in Health (MSQH) recommended a rejection rate target of less than 1%. Being a tertiary hospital receiving samples from various centres, optimising the rejection rate is a challenge. This study was conducted to identify the sample rejection rate and study the rejection profile in our laboratory. *Materials & Methods*: An audit on rejected samples from October 2022 to March 2023 was performed from archived laboratory information system (LIS) data. Percentage of monthly rejection rate, reasons for rejection and types of tests rejected were calculated based on all test requests received by the laboratory. Data of rejected in-house samples were further analysed to study the source of rejected samples. *Results:* The rejection rate ranged from 1.1 to 1.4% from October 2022 to March 2023. The common reasons for rejection were 'no sample received' (22.8±1.9%), haemolysed sample (22.0±3.2%) and clotted sample (20.6±2.7%). Some reasons for rejection were not clearly captured. The most common type of tests rejected were biochemistry (48.6 ±2.6%), haematology (32.5±2.5%) and serology tests (15.6±3.5%). The top three sources of samples rejected were from the Emergency Department (40.9±3.3%), Outpatient Department (12.9±4.8%) and Neonatal Intensive Care Unit (11.4±2.2%). *Discussion*: Our laboratory sample rejection rate exceeded the MSQH requirement. The profiling of rejected samples allows a more focused strategy to improve pre-analytical performance. A more comprehensive LIS setting is required to generate an explicit sample rejection profile.

CP22: Biochemical, clinical and molecular characterisation of Canavan disease in Malaysia: Our 10-year-journey

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Introduction: Canavan disease (CD), an autosomal recessive neurodegenerative disorder in the family of leukodystrophies is caused by ASPA gene mutation which encodes the enzyme aspartoacylase, responsible for hydrolysing N-acetylaspartate (NAA) in the brain. NAA can be identified by performing urine organic acid (UOA) analysis on gas chromatography mass spectrometry (GCMS). This retrospective study over the past 10 years highlights the spectrum of CD among Malaysian patients. *Materials & Methods:* The clinical records of three newly diagnosed aspartoacylase deficiency patients (Patients A, B, C) were retrospectively reviewed from 2013-2022. These patients were diagnosed from UOA analysis with the detection of NAA marker and further confirmed with molecular studies. *Results:* The patients (one male, two females) were all diagnosed before 12 months old. Two patients had a strong history of family consanguinity. Moderate to marked increased excretion of NAA in UOA analysis was seen in these patients. Clinically, these patients had similar features of hypotonia, developmental delay and macrocephaly. Molecular analysis revealed three different ASPA gene variants in all patients. Patient A has homozygous variant at c.634+1 G>T p.(?). Patient B harbours heterozygous variants at c.211C>T p.(Arg71Cys) and c.744G>C p.(Glu248His), while Patient C has homozygous c.509delT p.(Ile170Lysfs*8). In silico analysis predicted variants in Patients A and B as pathogenic while Patient C as likely pathogenic. The variants detected in Patients B and C were novel. *Discussion:* Detection of urinary NAA by GCMS and molecular analysis of ASPA gene is crucial in the early diagnosis of CD to differentiate from other types of leukodystrophies because most Canavan patients are severely affected with poor prognosis.

CP24: Hereditary Orotic Aciduria: Report of a rare case

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Introduction: Hereditary Orotic Aciduria (HOA) is a rare autosomal recessive disorder of pyrimidine metabolism caused by pathogenic variations of the uridine-5-monophosphate synthase (UMPS) gene that leads to megaloblastic anaemia, failure to thrive, susceptibility to infection and crystalluria. *Case Report:* A 2-year-old girl born to non-consanguinous parents presented with progressive developmental delay and failure to thrive. Routine blood investigations were in the normal range including blood ammonia. Inherited metabolic screening including plasma amino acids was performed and disorders of urea cycle defect were excluded. Persistent moderate elevation of urine orotate was seen on gas chromatography mass spectrometry (GCMS) with high performance liquid chromatography (HPLC) quantification of urine orotate of 65.33 mmol/mol creatinine. These results were highly suggestive of HOA. Molecular testing for UMPS gene detected a heterozygous variant c.178A>Cp.(Thr60Pro), classified as Variant of Uncertain Significance (VUS) using in silico prediction tools in accordance with The American College of Medical Genetics and Genomics (ACMG) guidelines. Further family screening revealed

that her father and younger brother also showed elevated excretion of urine orotic acid although they were asymptomatic. *Discussion*: This case highlights the significance of urine organic acid analysis on GCMS and urine orotate quantification using HPLC in the early diagnosis of HOA in three family members with persistent elevation in urinary orotic acid without hyperammonaemia. Despite the variant detected being classified as VUS, the presenting clinical symptoms and biochemical markers for the proband were favourable for the diagnosis of HOA. Genetic consultation for the family and early intervention will be beneficial to prevent complications such as megaloblastic anaemia and renal failure.

CP25: Adult-onset Methylenetetrahydrofolate Reductase Deficiency: Report of a Rare Case

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Introduction: Methylenetetrahydrofolate reductase (MTHFR) is a cytoplasmic enzyme that catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Mutations in MTHFR gene leads to hyperhomocysteinemia and homocystinuria due to abnormalities in the remethylation of homocysteine to methionine. It typically manifests in neonatal period and adult-onset is considered rare. *Case Report:* We report a case of a 31-year-old lady who first presented at the age of 14 years old with seizure and lower limb weakness. She was diagnosed with peripheral neuropathy with epilepsy and Vitamin B12 Deficiency at private hospital and was started on regular Vitamin B12 supplements. She was later referred to a tertiary hospital for further management of recurrent seizures. Serial plasma homocysteine was sent to determine the cause of Vitamin B12 deficiency and revealed significant elevation ranging 96-110µmol/L (N=4.6-8.1µmol/L). Brain imaging revealed significant cerebral atrophy with electroencephalogram showing diffuse encephalopathy. Her seizure episodes were controlled with anti-epileptic medication, but her plasma homocysteine level remained persistently high despite normalisation of Vitamin B12 level. Work-up for inborn errors of metabolism was only sent recently revealing low level of methionine, marked elevation of total homocysteine (236µmol/L) and normal findings on urine organic acids, collectively suggestive of MTHFR deficiency. Molecular confirmation is pending analysis. *Discussion:* Severe hyperhomocysteinemia (>100µmol/L) is essentially pathognomonic for inborn errors of homocysteine metabolism. This patient had prolonged history of severe hyperhomocysteinemia which should have raised the suspicion of a genetic defect earlier on. This case further highlights that inborn errors of metabolism can also manifest beyond the neonatal/infancy period.

CP26: Biochemical profiling of Multiple Acyl-CoA dehydrogenase deficiency (MADD): A case report

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Introduction: Multiple acyl-CoA dehydrogenase deficiency (MADD) or Glutaric Aciduria Type II deficiency is an autosomal recessive metabolic disorder which is a very rare disease reported in Malaysia and worldwide (1:200,000). *Case report:* A 56-day-old baby boy presented with respiratory distress, feeding intolerance and eczema. Laboratory findings were metabolic acidosis and hypoglycaemia along with elevated liver markers. He was further investigated for MADD. Several tests conducted including Analyses of Amino Acids, Organic Acids, Inborn Errors of Metabolism (IEM) Screening, Free and Total Plasma Carnitine. *Discussion:* IEM screening of dried blood spot demonstrated elevation of short, medium and long chains acylcarnitines with an increase of C10/C8 and C10/C10:1 ratios and free/total carnitine reported raised in acyl:free carnitine ratio while urinary organic acids revealed an increased excretions of 2-hydroxy glutarate, acylglycines and dicarboxylic acids which strongly suggestive of MADD. Plasma amino acids analysis showed non diagnostic profile. These findings were similar with known external quality assurance samples analysed in previous years. However, lab results of the second batch samples did not tally with the first batch. The discrepancy in the latter batch of samples could be due to several factors probably intermittent during acute metabolic decompensation. Thus, a sample was sent to an international referral laboratory for a mutation analysis and enzymatic studies. However, gene mutation was undetected yet awaiting for confirmatory studies on cultured fibroblasts to further confirm the diagnosis.

CP27: Early diagnosis of MTP/LCHAD deficiency by high-risk newborn screening prevent life-threatening metabolic decompensation: A case from a rural area

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Introduction: Mitochondrial trifunctional protein (MTP)/long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiencies are very rare inherited metabolic disorders (IMD) that prevent the body from converting certain fats into energy, particularly during periods without food or fasting. Early diagnosis and appropriate treatment of these disorders have the potential to improve outcomes and save lives. *Case report:* A 3-day-old term male infant, referred from a rural hospital to the state hospital for respiratory distress, initially presented with encephalopathy and hypoketotic hypoglycaemia with lethargy, hypotonia and poor response to stimulation. Further history revealed that one sibling died at 5-month-old, allegedly due to congenital cardiomyopathy. Elevated creatinine kinase and liver enzymes were observed in the routine examination. CSF, plasma, dried blood spot (DBS) on filter paper and urine were sent to our facility for IMD screening. Analysis of amino acids in the CSF and plasma showed no evidence of Non-ketotic hyperglycinemia (NKH). Acylcarnitines analysis

on the DBS showed elevations of long-chain acylcarnitines and long-chain hydroxyl-acylcarnitines with elevated C16-OH/C16 and C18-OH/C18 ratios. In addition, determination of organic acids in urine revealed mild elevation of 3-hydroxyl dicarboxylic acids supporting the acylcarnitines analysis report. Thus, MTP or LCHAD deficiency was highly suspected. For close monitoring, the infant was transferred to our facility and subsequently introduced with a diet low in fat and high in carbohydrates. *Discussion:* MTP or isolated LCHAD deficiencies are unable to distinguish by IMD screening. Therefore, the diagnosis can be further confirmed by mutation analysis of the *HADHA* and *HADHB* genes which takes approximately four weeks for the results to be out. LCHAD deficiency involves mutations that only affect the *HADHA* gene while MTP deficiency results from *HADHA* and/or *HADHB* gene mutations. Since the treatment for both disorders follow the same strategy, a preliminary report by the high-risk newborn screening is sufficient to justify the initial therapy as to prevent life-threatening metabolic decompensation.

CP28: Determination of acylcarnitines in plasma by liquid chromatography-Electrospray Ionization (ESI) tandem mass spectrometry for inborn errors of metabolism

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Introduction: Measurement of acylcarnitines is used to investigate patients for inborn errors of metabolism, specifically fatty acid oxidation disorders and organic aciduria. Newborn screening is currently performed on dried blood spots (DBS). Here, we evaluated the quantitation of acylcarnitines in plasma samples using tandem mass spectrometry. *Materials & Methods:* 10µl of plasma was mixed with internal standard containing mixture of deuterium-labeled internal standards acylcarnitines, then butylated before analyzed on a Waters Xevo TQ-S micro mass spectrometry using positive ionisation mode with multiple reaction monitoring method. *Results:* Free carnitine and 34 acylcarnitines were quantitated. The detection limit for all analytes was <0.008µmol/L and quantification limit was <0.03µmol/L. Total precision was <10% for free carnitine and most of the acylcarnitines, except few long chain acylcarnitines showed coefficient variation of <20% at high concentration. Recoveries were between 83.9% and 118%. *Discussion:* This method requires a small volume of sample, precise and reliable which could serve as an alternative sample or second tier testing to DBS to overcome some of the DBS's limitations.

CP29: High risk screening for Pompe disease in Malaysia: 15 years' experience

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Introduction: High risk screening for Pompe disease was introduced in Malaysia starting in 2008 using a modified method from Taiwan. Pompe disease (PD) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid α-glucosidase (GAA) due to mutations in the *GAA* gene. *Materials & Methods:* The samples were sent from high-risk patients who were suspected based on their clinical presentation such as poor sucking, respiratory problem, developmental delay, and cardiomyopathy. The biochemical diagnosis is based on GAA activity assays in dried blood spots (DBS) analysed by spectrofluorometer. Samples with abnormal results were repeated and 5mL of whole blood were sent to Molecular Diagnostic Unit for molecular confirmation. *Results:* A total of 6250 samples were screened from 2008 to June 2023, 10 cases were diagnosed positive (infantile form: n = 8; late-onset: n = 2). Repeat DBS was requested and about 73% of the recalled was normal on the repeat sample and did not require further action. The performance metrics for the test were acceptable (sensitivity: 95.6%, specificity: 99.8%, PPV: 20%, FPR: 0.15). *Conclusion:* GAA assay in DBS is poised to become a reliable, relatively non-invasive, and specific assay with the further advantage of a rapid turnaround time. Although PD is rare, early diagnosis and treatment can improve the outcome of patients and avoid lifelong impairments.

CP30: Epidemiology of mucopolysaccharidoses (MPS) in Malaysia: A three-year single-centred study

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Introduction: Mucopolysaccharidoses (MPS) are a group of inherited lysosomal storage disorders. MPS disorders result in an abnormal accumulation of complex carbohydrates (mucopolysaccharides or glycosaminoglycans) in skeletons, eyes, joints, skin, blood, spleen, liver, and brain. Eventually, this accumulation damages cells, tissues, and organ systems. We aim to obtain data about the epidemiology of the different types of mucopolysaccharidoses identified at the Institute for Medical Research. *Materials & Methods:* This study includes data collection from 788 samples for urine MPS between 2020 and 2022. All urine samples were analysed for glycosaminoglycans (GAG)s and characterised by high-resolution electrophoresis (HRE). Based on the clinical history and HRE results, whole blood was collected in ethylenediaminetetraacetic acid (EDTA) tube for enzyme analysis. We classified types of MPS, age of diagnosis, and gender from our Laboratory Integrated System (LIS). *Results:* 9 cases (5 male and 4 female) of MPS were identified with a median age of 4 years old and an age range of 2 days to 51 years. 8 were positive for MPS; (Type I = 2), (Type II = 2), (Type IVA = 1), (Type VI = 3). One patient had multiple sulfatase deficiencies. One patient with MPS type IV had homozygous c.857C>G p.(Thr286Arg) at Exon 8. All patients

were found to have dysmorphic features. *Discussion:* One in 100 high-risk patients was diagnosed with MPS being MPS type VI the most common among Malaysian patients. Dysmorphic features were the most common symptom. Molecular genetic testing is still recommended even though enzyme analysis is considered the gold standard for the diagnosis of MPS diseases.

3. Forensic Medicine

FM1: Association analysis between SARS-CoV-2 RT-PCR cycle threshold (CT) values, post-mortem computed tomography (PMCT) findings and its covariance factors at the National Institute of Forensic Medicine (NIFM)

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Introduction: NIFM experienced the impact of COVID-19 from January 2020 till June 2022 where 863 positive COVID-19 brought-in-dead (BID) cases were received. RT-PCR remains the gold standard as the detection technique for the SARS-CoV-2 virus. This study aimed to perform association analysis between CT values and the pneumonic changes of lungs and other covariance factors. *Materials & Methods:* This was a retrospective cross-sectional study involving convenient samplings of 187 positive COVID-19 BID cases with PMCT images available. Those cases with known positive COVID-19 results prior to death, RTK positive cases and decomposed bodies were excluded. Chi-square test, Kruskal Wallis test, and univariate analysis for the covariance factors including presence of pneumonia or crazy paving patterns, cause of death (COD) and vaccination status were performed. *Results:* There were significant differences between categories of CT values and the presence of pneumonia based on PMCT findings with 78.2% less than CT 30 whilst almost 50% more than CT 30 for the absence of pneumonia. The distribution of CT values had significant differences across categories of COD certified as "with COVID-19" (mean=27.06) and "due to COVID-19" (mean=23.81). The only significant univariate analysis of variances was the interaction of both presence of pneumonia and the vaccination status. *Discussion:* The vaccination status alone did not affect the distribution of CT values. The CT values were not definite in reflecting the presence of pneumonia but it tended to be lower in those cases. These could be more convincing for the certification of death with "due to COVID-19" by the forensic medical officers and specialists.

FM2: Geometric morphometric analysis based on sacrum landmarks among Malaysian population

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Introduction: Biological profiling in the anthropological approach comprises of sex, ancestry, stature and skeletal age estimation. The 3D digitisation includes computed tomography (CT) scan has been applied for 3D geometric morphometrics (GMM) in concurrent with statistical analysis. This study aims to conduct a GMM analysis to explore the shape variations on sacrum within the Malaysian population. *Materials & Methods:* A total of 320 subjects were collected at Kuala Lumpur Hospital according to sex, ancestry and age among three main ethnicities. The segmented sacral bones from CT images using Mimics Research 17.0 software were marked with 19 raw points via IDAV Landmark 3.0 software. Their coordinates were being extracted into Notepad++ 7.6.3 software and analysed with MorphoJ 1.06d software. GMM analysis showed that the utmost degree of variations was observed on the transverse diameter of the S1 body, alae dimensions and auricular surfaces. *Results:* Sex discrimination function with cross validation success rate was between 84.47% up to 92.45%. Discrimination functions with cross validation success rate between Chinese and Indian ranged from 64.22% to 83.02%. Elderly individuals had bigger S1 body dimensions, alae antero-posterior dimension and shorter sacral height compared to adolescents with varies cross validation success rate up to 84.78%. *Discussion:* Males had relatively more curved sacrum, longer sacral height and auricular length, bigger S1 body dimensions but narrower alae compared to females. Chinese had generally higher sacral basal width and sacral height compared to Malay and Indian. This population-specific study is valuable for Malaysian experts in analysing the sacrum for biological profiling.

FM3: An unfortunate child

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Introduction: Forensic pathologist conducts medico-legal autopsies as directed by the investigating police officer to look into cases of sudden, unexpected death. In forensic practices, sudden death from an unidentified brain tumour is rarely seen or suspected. The most common causes of central nervous system (CNS) pathologies encountered in our practices include severe trauma, haemorrhage, epilepsy, and infection. Here, we present a case of paediatric glioma identified at autopsy together with histopathological examination and immunohistochemical results. *Case report:* A girl was found dead at home. The autopsy revealed an intra-axial and circumscribed tumour at the left frontal lobe with focal haemorrhagic and necrotic areas. Microscopically, the tumour showed varied cellular density. The tumour cells have round to oval nuclei with speckled chromatin. The vascular pattern, dystrophic calcification and clear cell change are frequent features of supratentorial ependymoma. *Discussion:* The diagnosis of ependymal tumours should now be classified according to a combination of histopathological, molecular features and anatomical site. Death usually occurs due to the direct effect of the tumour on

the surrounding brain or increased intracranial pressure. Forensic contribution in diagnosing the disease is paramount for future detection by the physician.

FM4: Atypical cause of heart attack in adolescent

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Introduction: Heart attack led to sudden death in adolescent is very rare. It's usually due to congenital heart disease or channelopathy. We reported an atypical case of an adolescent boy with fibromuscular dysplasia of the coronary arteries that lead to sudden cardiac death. *Case report:* 17-year-old boy complaining of chest pain and dyspneoa few hours before he collapsed and succumbed to death. Police brought him to hospital for autopsy. Heart was not enlarged. Left anterior descending artery and right coronary artery demonstrated dilated lumen with total luminal occlusion by thrombus and thickening of the vessel wall. Cut sections of the heart showed area of fibrosis at anterior and posterior left ventricle. Histological examination of the heart displayed prominent thickening of the intimal layer of coronary arteries with organized thrombus. There were also areas of fibrocollagenenous tissue of the myocardium with the intramyocardial arteries showing prominent thickening of the intimal layer and narrowing of the lumen. Histological examination of the kidney also displayed prominent thickening of the intimal layer of renal arteries. The histological findings of the coronary arteries, intramyocardial arteries and renal arteries were suggestive of fibromuscular dysplasia. Cause of death was concluded as fibromuscular dysplasia of coronary arteries complicated with thrombosis. *Discussion:* Fibromuscular dysplasia (FMD) is a non-atherosclerotic arterial disease that is characterized by abnormal cellular proliferation and distorted architecture of the arterial wall. FMD involving the coronary arteries is an uncommon but important condition that can present as acute coronary syndrome and potentially sudden cardiac death.

FM5: Missing the 'Swirl': An autopsy case of venous extradural haemorrhage

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Introduction: Head injury is the single largest contributor to trauma center deaths. Overall mortality of patients with head injury (18.2%) was three times higher than if no head injury occurred (6.1%). An extradural haemorrhage (EDH) occurs in up to 15% of all fatal head traumas. Delay in its diagnosis and treatment increases the morbidity and mortality. *Case report*: A 29-year-old motorcyclist involved in a vehicular crash and sustained occipital extradural haemorrhage with mass effect. Craniotomy and evacuation of clot was done and patient regained full consciousness. On Day 4 post surgery patient developed headache and subsequently collapsed dead approximately 24 hours later. A repeat CT brain on Day 4 post surgery showed an extradural haemorrhage with swirl sign on left temporoparietal region that was unnoticed by the clinician. Autopsy had confirmed this finding. *Discussion:* The less common cause of EDHs is due to venous bleeding which is up to 10% following the laceration of a dural venous sinus. In this case, due to the fracture of the occipital bone and petrous part of temporal bone, the transverse venous sinus and superior petrous venous sinus could have been lacerated. On the other hand, the surgery as well could have possibly lacerated those venous sinuses. As the EDH develops more slowly in dural sinus tear and so the clinical manifestations. The swirl sign, an ominous sign which indicate an expanding EDH with ongoing active bleed. An error of clinical judgement had occurred in relation to his death.

FM6: Death by fecaloma: A grim reminder of the risks associated with neglected bowel obstruction

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Introduction: Fecaloma is a condition characterised by the formation of a hardened mass of stool in the large intestine or rectum due to impacted and compacted faecal matter over time, leading to a blockage that prevents normal bowel movements. *Case report:* This case report describes the death of a 14-year-old female patient who presented with abdominal pain and distention, loss of appetite, and severe constipation. Despite being advised to seek further medical care, she resorted to self-medication with Voltaren, Librax, and Simethicone. Over the course of 7 days, her condition deteriorated, leading to her demise. Postmortem findings included cachexia, pale skin, severe dehydration, and marked abdominal distension. Autopsy revealed an 8.5 cm diameter consolidated fecaloma obstructing the rectum completely, causing a dilatation in the small and large bowels, the largest dilatation being in the sigmoid colon above the impaction point, reaching nearly 20 cm diameter. No ischemic bowel changes or gut leakage were observed. Toxicology showed Chlordiazepoxide in the stomach and gallbladder contents. Histopathology demonstrated emphysematous lung changes, chronic small and large intestinal inflammation, mild kidney ischemia. No chemical analysis was done. *Discussion:* The cause of death was attributed to the intestinal obstruction, which likely led to electrolytes imbalance or severe respiratory distress due to increased intraabdominal pressure impeding diaphragmatic movement. This case underscores the importance of timely medical intervention and highlights the potential consequences of self-medication and delayed treatment in patients with gastrointestinal symptoms. Education and awareness programs are needed to improve healthcare-seeking behaviours in underserved populations, particularly in rural areas.

FM7: Pattern of deaths in paediatric population - An autopsy-based study of southern region of Selangor state

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Introduction: The mortality rate of infants, children and adolescents varies substantially from one region to another. The aim of this study is to describe the pattern of autopsy cases of children under the age of 18. *Materials & Methods:* The study was done retrospectively in southern regions of Selangor state to assess the pattern of paediatric deaths among total paediatric autopsies conducted from January to June 2023. All autopsy cases of neonates up to the adolescent age group were studied. *Results:* During the 6 months study period, 47.9% were males and 50% were females in total 48 paediatric autopsies. The ethnic group comprised Malay (58.3%), Chinese, Indonesian, unknown group (10.4% each), Burmese (6.3%) and Indian (4.2%). On distribution of cases, 65.5% were natural death, 22.9% were accidental death, suicidal and homicidal death were recorded in 8.3% and 6.3% respectively. Among the natural causes, the commonest diseases were pneumonia (37.9%), congenital heart abnormalities (17.2%) and hypertrophic cardiomyopathy (10.3%). *Discussion:* Autopsies of paediatric death caused by natural disease account for a significant percentage. The number of deaths by unnatural causes rises with the age of children and adolescents. The suicides of young people are given particular attention, and there are several contributing factors, including social interactions and mental health problems. However, teenagers don't have the same social relationships as adults. Understanding the underlying epidemiological changes would enable in improving preventive measures and strategies planning in the healthcare system.

FM8: Unusual cause of sudden death in toddler - Ascending meningitis secondary to Pott disease

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Introduction: Pott disease, also known as tuberculous spondylitis. It is an extrapulmonary tuberculosis which manifests as a combination of osteomyelitis and arthritis. *Case report:* 22-month-old boy who was found dead while sleeping and had a low-grade fever the day before. Clinically, his developmental milestone was up to age. However, his mother observed he had a tendency to lean to the right when he walked. Postmortem examination showed solitary, well circumscribed firm mass, 2.7x2.5x2cm, that arose from the right side of 5th to 8th thoracic vertebrae. Histopathological examination showed multiple caseating granuloma with Langhan giant cell infiltration and positive acid-fast bacilli detected. Hence, the tuberculous spondylitis is confirmed. The histopathological examination of the cerebral cortex and spinal cord showed meningitis. *Discussion:* The presentation of Pott disease in a toddler may be subtle, but its complications can be devastating and cause sudden death.

FM9: Is this synthetic cannabinoids-related death?

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Introduction: Synthetic cannabinoids (SC) have stronger binding affinity with cannabinoid receptors, renders it exceeds cannabis potency and exhibits effects of more typically associated with psychostimulants. *Case report:* A 19-year-old man, a person with disability (slow learner) exhibits abnormal behaviour after he smoked on a so-called 'mushroom' flavoured vape. He appeared confused and agitated, recklessly riding his motorcycle, hitting a few cars along the way before falling down and subsequently ran away into heavy rains. Approximately 36-hours later, his body was found in a water-filled drain. Autopsy showed a decomposed body with no significant disease process or injury. Histological examination of lungs showed decomposition with no emphysematous changes or foreign bodies seen. Analysis of stomach contents, liver and kidney tissues were negative for common drugs. Toxicological analysis of the confiscated alleged vape kit was positive for MDMB-4en-PINACA and EDMB-4en-PINACA. *Discussion:* It is a challenging task for timely detection of SC in biological samples. Not all cases subjected to the same scope of analysis and SC detection could have been missed in potential cases, particularly in vape users if we were unaware of it. The SC usage that was associated with lethal outcomes have been reported. However, determination as to its cause and manner of death has not been clearly defined due to the lack of controlled studies and the inability to correlate the SC concentration to its effect. The cause of death in this case is unascertainable limited by decomposition.

FM10: Paediatric primary peritonitis: A postmortem review

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Introduction: Primary peritonitis, also known as spontaneous bacterial peritonitis, is a bacterial infection within peritoneal cavity in the absence of focus intra-abdominal source. It is rather uncommon phenomenon in paediatric and, as in our case, a rare cause of death. *Case report:* We presented a case of 6-year-old girl who was brought in dead to a district hospital. Initially, she had upper respiratory tract symptoms followed by generalized abdominal pain for 2 days with multiple episodes of vomiting prior to her death. She had history of visiting a general practitioner and was treated as viral infection. No history of recent trauma. Otherwise, she had no known medical illness with no history of prolonged hospital admission. There were no visible injuries on the body upon external assessment. Further examination revealed presence of 500 ml purulent peritoneal fluid with evidence of peritonitis. Additionally, slough deposits were observed on the peritoneal linings and intestines. The appendix was not inflamed. There was no evidence of perforated viscus or pancreatitis. The reproductive

organs appeared normal. Histological examination supported these findings. Further investigations revealed persistence growth of Escherichia coli in the blood, peritoneal and spleen tissue culture. *Discussion:* Although the mortality is low due to the advent of antibiotic, death still occurred in cases with delayed diagnosis. This is given to its non-specific symptoms and absence of predisposing factors commonly associated with peritonitis. This case highlights specific risk factors and pathological findings associated in the case of paediatric primary peritonitis.

FM11: Lung chronicles: decoding granulomatous disease; role of molecular study

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Introduction: Granuloma alone is a nonspecific histopathological finding, rather it comprises a group of disorders which have a wide spectrum of pathologies. The integration of histological analysis and molecular study is crucial in concluding a case in the field of forensic pathology. *Case report*: A 43-year-old Malay gentleman was found unconscious at his home. Reportedly, he has no known medical illness but was an intravenous drug user and had multiple histories of prison detention, though he was not under custody at that moment. He had a short history of fever and shortness of breath. External examination revealed a cachexic, medium body-built with no marks of injury. However, upon opening the chest, there was generalized adhesion of the pleura with cavitations of bilateral lungs and copious amounts of pus-like secretions. Histological analysis of the lung sections showed presence of few multinucleated giant cells. *Discussion*: Presence of lung cavitations grossly, together with giant cells with or without granuloma histologically, were frequently associated with mycobacteria infection. This has not always been the case, particularly in the case reported above as the sample sent for molecular study did not detect mycobacteria. What is highlighted under the microscope will somehow need to be further investigated with molecular study, either to nullify or confirm the preliminary findings.

FM12: Silent clues: decoding autopsy case of subinvolution of placental site

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Introduction: Secondary postpartum haemorrhage (PPH) accounts for 1% of maternal death and subinvolution of the placental site (SPS) is one of its uncommon aetiologies. *Case report:* A 34-year-old woman (Para1) was brought-in-death 14 days post vaginal delivery to the emergency department. Her delivery was uneventful. Antenatally, she had gestational diabetes and good glycaemic control. She was asymptomatic postnatally and stated having chills, light-headedness and vomiting two days before her death. Unfortunately, her husband was unable to quantify the amount of vaginal bleeding during the postpartum period. At autopsy, her sarong and undergarment were soaked with blood, and her body was pale. The underlying SPS was identified from the autopsy. Endometritis and urinary tract infections were also present. *Discussion:* Subinvolution of the placental site can cause significant delayed postpartum haemorrhage and if undetected may result in death. SPS is defined as delayed or inadequate physiological closure and sloughing of the superficial modified spiral arteries at the placental site (the failed process of normal involution). The diagnosis of SPS was confirmed histologically by the presence of endovascular extravillous trophoblasts and clustered myometrial arteries that were dilated and partly occluded by old and new thrombi. Although the cause of subinvolution is not known, this process may manifest an abnormal interaction between foetal-derived trophoblasts and maternal tissue. Subinvolution is an important process to recognise, as it implies an idiopathic cause of delayed postpartum bleeding. The diagnosis of SPS can be challenging as it requires a detailed autopsy including histology.

FM13: Mesenteric haematoma as a rare complication of acute pancreatitis: a case report

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Introduction: Mesentery haematoma is an uncommon and potentially life-threatening complication of acute pancreatitis in the absence of any external abdominal trauma. Despite the normal appearance of the pancreas during an autopsy, the possibility of acute pancreatitis cannot be totally excluded especially in the presence of a mesentery haematoma. *Case report:* A 40 years lady with no known premorbid presented with abdominal pain, vomiting and loose stool for two days. She was treated for gastritis prior to death. The autopsy examination showed no fatal external injuries. Abdominal examination exhibited mesentery haematoma. Although the pancreas appeared grossly normal; histopathological examination of the pancreas showed evidence of necrotic tissue with adjacent inflammatory infiltrates, haemorrhage and fat necrosis. Postmortem serum amylase revealed twenty folds increment from the normal value. *Discussion:* Acute pancreatitis is an inflammatory disease which can be associated with significant complications and these can be categorized into either early or late and local or systemic. Acute pancreatitis can be the cause of sudden unexpected death where haemorrhagic pancreatitis holds higher mortality rates. Nevertheless, the absence of typical gross pathological findings on the pancreas during autopsy may defy the diagnosis of acute pancreatitis. Hence, a higher suspicion rate towards pancreatitis in the presence of mere surrounding tissue haematoma will help in determining the underlying pathology. Furthermore, postmortem serum amylase in a fresh body would have some potential benefit in providing supportive evidence along with the histopathological changes towards determining the final cause of death especially in a case of acute abdomen presentation.

FM14: An uncommon lethal duo: inhalation of volatile hydrocarbons and plastic bag asphyxia

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Introduction: Forensic pathology encounters various cases of asphyxia, encompassing chemical and mechanical asphyxia. The occurrence of death due to a combination of chemical asphyxia, such as liquified petroleum gas and plastic bag asphyxia, is uncommon. *Case report:* A 44-year-old man was allegedly found dead inside his bedroom with his head covered with a plastic bag and connected to a cooking gas cylinder tank. There was pornographic paraphernalia present inside the mobile phone beside him. *Discussion:* Investigating asphyxia-related deaths is crucial in understanding the mechanisms behind this fatality. The case at hand raises questions about autoerotic practices, as the absence of clear suicidal indicators points towards the possibility of accidental death during a sexual activity involving the co-occurrence of hydrocarbon inhalation and plastic bag asphyxia.

FM15: Analysis of repeat rejected urgent laboratory test requests: A descriptive data study

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Introduction: In line with the Malaysian Society for Quality in Health (MSQH) Hospital Accreditation Standards, laboratories must ensure a short laboratory turn-around-time (LTAT). However, laboratory rejections including for urgent test requests are unavoidable commonly due to pre-analytical non-conformity. *Materials & Methods:* This was a cross-sectional study taking place in a tertiary hospital pathology laboratory based in Kuala Lumpur involving December 2022 in-house urgent test requests. The data extracted from laboratory information system (LIS) consists of two biochemistry test profiles (liver function test (LFT) and renal profile (RP)) and three individual analyte requests (calcium, magnesium, phosphate and C-reactive protein (CRP)). The repeated rejected urgent tests were defined as new samples that were re-sent within 24 hours post rejection. *Results:* From 70 rejected urgent tests requests, 57(81.4%) were repeated while the remaining 13 (18.6%) were not repeated. 14 (77.0%) and 16 (75.0%) rejected urgent LFT and RP were respectively repeated. 6(85%) of rejected urgent calcium, magnesium and phosphate were also respectively repeated. Overall, 10 (14.3%) tests were repeated only after 3 hours. The interval following rejection to arrival of new samples varies from 0.3hours to up to 12.8 hours. The most prevalent reason for urgent test rejection was haemolysis 64 (91.5%), followed by no sample received 6 (8.5%). *Discussion:* Nearly 20% of the unrepeated rejected urgent test and the long hours of repeat interval do not justify the purpose of an urgent test request. Reinforcement of urgent test indication in the request form, and improvisation to the readily available laboratory rejection notification workflow could be part of interventions to tackle this issue.

FM16: Postmortem human rabies diagnosis: A case report

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Introduction: Rabies in Malaysia had been a public health concern as the outbreak of cases need to be contained and eliminated as soon as possible. As rabies is incurable and highly fatal, preventive measures such as immunization for animals and post-exposure prophylaxis for humans are crucial. The incubation period for rabies virus is usually between 1 to 3 months and the classical symptoms and signs may be absent after a long period of time. Hence, the awareness of the disease amongst forensic practitioners is important in diagnosing rabies in postmortem case. *Case report:* A 39-year-old male was found unresponsive at home by his mother and subsequently declared dead by paramedics at the scene. He had a history of dog bites and scratches 2 weeks prior to his death. At autopsy, the external examination revealed multiple scars at the head, chest and upper limbs with ulcers at both lower limbs. Fresh dog bites were not visible. Internally, the brain was grossly unremarkable. The brain tissue was sent to the laboratory for PCR rabies testing and yielded positive result. Histopathology of the brain revealed changes commonly associated with rabies. *Discussion:* This case highlighted the role of forensic pathology in diagnosing rabies infection. Even without typical external and internal autopsy findings, the circumstances of death had warranted investigation of rabies and prompted initiation of relevant public health preventive measures. Following notification of disease to authority, several public health initiatives were performed to control spread of disease.

FM18: A lethal synergy: Microsporidia and HIV's deadly dance

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Introduction: Microsporidia and HIV are two distinct yet interconnected entities that have significant impacts on human health. Microsporidia are opportunistic intracellular parasites, responsible for causing opportunistic infections in immunocompromised individuals, such as those with HIV/AIDS. Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the immune system, weakening the body's defense mechanisms, making it more vulnerable to various infections and illnesses. *Case report:* We report a case of a 44-year-old male. He was allegedly found unresponsive in his bathroom. He experienced an increasing

frequency of abdominal pain, diarrhoea, weakness and cramping of muscles, and lethargy for a 2-month duration before his demise. His symptom did not improve despite seeking treatment at a nearby clinic. On autopsy, the body was cachexic and dehydrated evidenced by a sunken eyeball, reduced skin turgor, and vitreous urea of 10.9 mmol/L. HIV was positive for rapid test, and further confirmatory tests were done by PA and ECLIA methods. Internal examination showed hyperaemic mucosa of the intestine. Histology of the intestinal mucosa revealed predominantly autolytic changes of the villi with blunting surrounded by moderate infiltrations of chronic inflammatory cells. *Microsporidia spp* spores with a characteristic belt-like stripe were detected in stool using Gram Chromatrope Kinyoun stain. *Discussion:* Detecting microsporidia in postmortem samples can serve as a crucial indicator of advanced immunodeficiency. It is also important to understand the relationship between these two entities is vital in managing the infections they cause and devising effective strategies to combat their debilitating consequences on global health.

FM19: Primary Ewing sarcoma of the left atrial appendage: A case report.

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Introduction: Primary cardiac tumour are rare entities with estimated prevalence is 1:2000 autopsies as compared to secondary tumour with secondary/primary ratio of 20:1. Only quarter of it are malignant and usually sarcoma. Ewing's sarcoma of cardiac origin which is thought to be derived from neural crest cells is much rarer with only a few reports described in the literature. *Case report*: A 37-year-old male who was initially presented with difficulty in breathing in which echocardiography showed cardiac tamponade. Further diagnostic imaging work-up revealed cardiac mass with no other primary and he was planned for resection unfortunately the tumour was deemed inoperable. Biopsy taken came back as Ewing sarcoma of left atrial appendage. He received chemotherapy regime but the tumour did not downsize and he eventually passed away. Post-mortem examination revealed tense sanguineous pericardial effusion with left atrial appendage tumour measuring 12cmx8cm invading the left ventricle's epicardium. *Discussion:* Malignant primary cardiac tumour has a dismal prognosis with no clear definite treatment. Symptoms presentation is dependent on tumour location and size rather than histological characteristics. Left atrial sarcoma tend to be more solid and less infiltrative than right sided sarcoma. Patient usually presented with symptoms of blood-flow obstruction and eventually congestive heart failure. Although the tumour in our case originated from the left atrial appendage, the tumour behaviour was quite aggressive, infiltrating the epicardium of the left ventricle and causing large and tense pericardial effusion, which ultimately resulted in the patient's death.

FM20: Laryngeal edema in amniotic fluid embolism (AFE) death

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Introduction: AFE, a rare occurrence with an unknown exact pathophysiology poses different clinical manifestations, of which can be classified into; classical, anaphylactoid and disseminated intravascular coagulation subtypes. *Case report:* A 35-year-old primigravida at 40-week gestation with underlying gestational diabetes mellitus on diet controlled, had no known history of allergy, experienced sudden onset of lower abdomen discomfort while having conversations. She suddenly became unresponsive with leaked clear liquor. She was brought to an emergency setting where she was pronounced death on arrival, approximately 1-hour after the onset. Autopsy, conducted 12-hour later, revealed a gravid abdomen contained a term, 3 kg baby with attached umbilical cord and unremarkably adhered placenta to uterus. Amniotic membrane rupture seen and cervix was oedematous. The larynx was oedematous and hyperaemic with narrow vocal cord opening. The lungs were oedematous. The other organs were unremarkable. Histological examination confirmed the presence of foetal squames in the pulmonary vessels and venules of the cervix. Significant mast cells and eosinophils infiltration seen in the laryngeal mucosa Serum tryptase 6.86 mcg/L. *Discussion:* Laryngeal oedema is an abnormal accumulation of fluid and swelling in the tissues of the larynx commonly associated with laryngeal injuries and allergic causes. Two published hypotheses for the cause of AFE-associated reactions namely; an effect of the amniotic fluid itself (its components) or a host idiosyncrasy ("hypersensitivity" reaction). The laryngeal oedema in this lady was best explained by 'anaphylactoid syndrome of pregnancy'. Despite that, other possible causes of laryngeal oedema should not be overlooked.

FM21: Acute haemorrhagic pancreatitis: sudden death in a child

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Introduction: Sudden unexpected death forms the core subject of medicolegal investigation that if occur in an apparently healthy individuals, an autopsy would shed light regarding the cause of death. Attributing deaths due to acute haemorrhagic pancreatitis in a paediatric age are fairly uncommon. The spectrum of acute pancreatitis ranges from mild inflammation to severe haemorrhagic and necrotizing pancreatitis complicated by respiratory, renal, or hepatic failure, and even death. *Case report:* Herein, we describe a medicolegal autopsy of sudden unexpected deaths of a 9-year girl, who had multiple episodes of vomiting and abdominal pain one day prior to her demise. She became less responsive and was collapsed during the journey to the hospital. An autopsy was carried out on the next day certified her death were from acute haemorrhagic pancreatitis. *Discussion:* The pathology and histology of acute haemorrhagic pancreatitis will be discussed. This case underscores a high suspicion for acute pancreatitis in children presenting with acute abdomen to institute prompt intervention. Timely diagnosis can mitigate complications and forestall mortality associated with haemorrhagic pancreatitis.

FM22: Applications of post-mortem genetic screening on heart diseases in autopsy cases: A scoping review
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Introduction: Sudden cardiac death (SCD) is a tragic event that occurs unexpectedly and it is often attributed to underlying cardiac abnormalities. Post-mortem genetic screening has emerged as a promising tool for identifying potential genetic factors contributing to SCD. This scoping review aims to evaluate the existing evidence on the utilisation of post-mortem genetic screening in cases of SCD that underwent autopsy. *Materials & Methods:* A comprehensive literature search was conducted across various electronic databases. It was conducted using the framework suggested by Arksey and O'Maley. A comprehensive search was performed to identify published works and literature. The inclusion criteria for the search were articles in English from 2013 until 2023. The inclusion criteria were set to encompass studies that investigated the application of post-mortem genetic screening in autopsied cases of SCD, irrespective of age or geographical location. *Results:* The selected articles were critically appraised to assess their methodological quality and to extract relevant data pertaining to the type of specimen used, post-mortem genetic screening techniques employed, the genes investigated, and the findings concerning potential genetic contributors to SCD. *Discussion:* The findings of this systematic review highlight the increasing adoption of post-mortem genetic screening in SCD cases and its potential significance in elucidating underlying genetic factors that may contribute to these untimely deaths. The studies reported diverse genetic variants associated with inherited cardiac conditions, including channelopathies, cardiomyopathies, and other heritable cardiac disorders. In conclusion, post-mortem genetic screening has emerged as a valuable tool in the investigation of SCD cases during autopsy.

FM23: Systemic septic embolism due to *Proteus mirabillis* renal abscess in a lady with olfactory-groove meningioma, WHO grade 1
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Introduction: Proteus mirabilis interacts specifically with the host immune system to determine its resultant virulence. Like other Proteus species, it releases endotoxin that triggers exaggerated host inflammatory response with 20% to 50% incidence of mortality. Needless to say, immunocompromised patients have even higher risk for sepsis or prolonged infections. *Case report:* A 42 years old female diagnosed and operated for olfactory-groove Meningioma, about a year back, was later brought back to the emergency, dead. At autopsy, the gross and histological examination of brain does not refute the underlying disease. Further examination showed grossly unremarkable solid organs except for the kidneys where there were shallow cortical scars and fine granularity seen on bilateral parenchymal surfaces. Cut-section of the right kidney showed focal area of yellowish spot in the renal parenchyma which histologically proved to be a focal area of abscess formation with few septic emboli seen in the interstitial and glomeruli. Interestingly, histological examination of other organs including the brain, heart, lungs, liver and spleen also showed presence of septic emboli. The findings were concluded definitively when the microbial investigations isolate ESBL Proteus mirabilis in many of the cultures. *Discussion:* Detailed clinicopathogenesis of the case will be further elaborated. This report aims to share the interesting findings in a lady with a rarely fatal underlying disease which actually predisposes her to fatal infections instead.

4. Genetic Pathology

GP1: An epilepsy patient with WWOX-related epileptic encephalopathy (WOREE) syndrome: A case report
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Introduction: The WWOX gene is a tumour suppressor gene, when mutations occur, it can cause a seizure-related brain disorder known as WWOX-related epileptic encephalopathy (WOREE) syndrome. Most WOREE syndrome patients experience seizures within the first two months after birth, although some children achieve a certain level of seizure control after a period of time, most drugs have poor efficacy in relieving seizures. Therefore, early genetic testing should be performed to determine the cause. *Case report:* A one-year-old male infant experience the first seizure attack one month after birth, with symptoms including spasmodic limb paralysis, upward eye deviation, and clenched teeth. After receiving antiepileptic medication and a ketogenic diet, there was no improvement after one year. An ophthalmological examination revealed optic neuropathy, neuroimaging showed poor development of the corpus callosum, cortical atrophy leading to enlargement of the ventricles and subarachnoid space, and underdevelopment of the cerebellum. Whole-exome sequencing (WES) is used to identify WWOX gene mutations that cause the disease, a mutation was also found in the father's WWOX gene (c.160C>T p. (Arg54*)) and in the mother's WWOX gene (c.796_797insGCTGCC:p.Cys266 delinsCCArg). These mutations in the WWOX genes from both parents caused changes in the protein structure and function of the WWOX gene, leading to the development of WOREE syndrome. *Discussion:* In difficult cases of treating epilepsy in infants and young children, genetic factors should be suspected and genetic sequencing should be performed. Currently, treatment for WOREE syndrome mainly focuses on symptom management, but there are many ongoing studies on treatment methods.

GP2: Tumour-suppressive role of circSPINT2 in Osimertinib-resistant non-small cell lung cancer (NSCLC) cells

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Introduction: Prolonged 1st/2nd generation EGFR-TKI treatments lead to selective drug pressure and secondary EGFR T790M mutations in NSCLC patients. Third generation EGFR-TKI (Osimertinib/AZD9291) effective at first, but resistance arises within 12 months, indicating complex tumour evolution during therapy. Transcriptomic advancements highlighted the involvement of non-coding circular RNAs (circRNAs) in drug resistance and cancer progression. Higher circRNAs stability than linear RNAs in blood plasma suggests their potential as predictive and prognostic biomarkers, but their role in Osimertinib resistance mechanism remains uncertain. Hence, in this study, we aimed to investigate the function of novel circular RNA (circSPINT2) and its regulatory mechanism in Osimertinib resistance. *Materials & methods:* CircSPINT2 was detected in Osimertinib-resistant cell lines (OR) using circRNA sequencing (circRNA-Seq). CircSPINT2 properties were assessed using qRT-PCR, Sanger sequencing, and RNase R treatment. Biotinylated circRNA pull-down assay, miRNA-seq, and in-silico analysis were employed to identify circSPINT2 downstream miRNA-mRNA regulatory axis. Subsequently, Osimertinib-resistant mouse xenograft model was established to explore the molecular mechanisms associated with both circSPINT2 and Osimertinib resistance. *Results:* Transcriptomic analysis showed circSPINT2 was downregulated in OR cells. *In-vitro* analysis indicated high circSPINT2 increased tumour suppressor RBP1 expression by sequestering oncogenic hsa-miR-1296 further improving Osimertinib sensitivity. Molecular and histologic analysis of subcutaneous xenograft tumours corroborated our *in-vitro* results. *Discussion*: Our study provided evidence of circSPINT2 acting as a tumour suppressor, effectively enhancing Osimertinib sensitivity through modulation of the hsa-miR-1296/RBP1 axis. Remarkably, circSPINT2 may serve as a prognostic and cancer biomarker to monitor Osimertinib resistance in NSCLC patients.

GP3: EGFR signalling pathway mutations in colorectal cancer: Experience from a new laboratory

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Introduction: The evaluation of epidermal growth factor receptor (EGFR) signalling pathway gene mutations such as *NRAS*, *KRAS*, *BRAF V600E*, *PIK3CA* and *AKT1* is decisive in the era of targeted therapy for colorectal cancer. The aim of this study is to determine the prevalence of these mutations and to categorise the mutation profiles in our local patient cohort. *Materials & Methods:* Thirty-three formalin fixed paraffin embedded specimens of histologically confirmed colorectal adenocarcinoma between 2022 and 2023 were selected for DNA extraction using convenience sampling, irrespective of the stage of cancer. The extracted DNA were then subjected to real time PCR amplification using EntrogenÒ Colorectal Cancer Mutation Detection Panel kit. The clinicopathologic parameters of the samples were retrieved from the medical records. *Results:* In our study population, the median age of presentation at diagnosis is 61 years old, with a male preponderance, (male: female ratio of 1.54:1). Out of the 33 samples, the prevalence of *NRAS*, *KRAS* and *PIK3CA* mutations were 57% (19), 79% (26) and 48% (16) respectively. Only one patient harboured the *BRAF V600E* mutation whilst 3 patients had the *AKT1 E17K* mutations. For *NRAS* mutations, the most common mutation is on exon 4 (codon 146) (79%) whilst for *KRAS* mutations, multiple mutations involving exon 2 (codon 12) are prominent. In *PIK3CA*, the mutation involving Exon 9 (Codon 542/545) is most common. All mucinous adenocarcinoma in our sample had *KRAS* exon 2 mutation. *Discussion:* The individual prevalence of the mutations is comparable to the prevalence reported in literature. As the presence of RAS oncogene is significantly associated with unresponsiveness towards EGFR monoclonal antibodies (e.g. Cetuximab), the prognostic significance of each individual mutation could be established in future prospective studies.

GP4: Two cases of 9p22 deletion in northern Malaysia

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Introduction: Constitutional deletion of the 9p region is a rare genetic disorder. The deleted breakpoint can be variable, but in many reported cases, it is in the region of 9p22 to 9p24. People with this missing region are said to have deletion 9p syndrome or Alfi's syndrome. *Case report:* Here we report, to the best of our knowledge, the first two cases of deletion 9p22 in the northern region of Malaysia. The first case is a female, 4 years old. She is the first child born with features such as a prominent forehead, an upturned nose, macrocephaly, hypotonia, and global delay. The second case is a female, 1 year old. She is the second child of two siblings and has features of a syndromic face, low-set ears, a flat nasal bridge, an almond-shaped eye, and hypotonia. Cytogenetic analysis for both cases revealed deletion at the 9p22 region. *Discussion:* The 9p deletion syndrome of Alfi's syndrome is reported to occur in one in 50,000 newborn babies, of which two-thirds are girls. Phenotypic characteristics like developmental delay and characteristic facies are common, and other abnormalities have been

reported, for instance, cardiac anomalies. Due to the low incidence and lack of high-resolution genotyping and phenotype data, this syndrome has various unresolved features. Thus, today's modern genomic technologies such as chromosomal microarray (CMA), whole-genome sequencing (WGS), and optical genome mapping (OGM) will be able to characterise the 9p deletion perfectly in order to achieve precision genomics and contribute to the development of individualised care.

GP5: A case report of a tertiary trisomy: Emanuel syndrome

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Introduction: Emanuel syndrome (ES) is a rare genetic disorder caused by the presence of an extra chromosome; derivative chromosome 22 [(der)22]. It causes multiple congenital anomalies and severe developmental delays. As of date, there are only 400 reported cases in literature. *Case report:* This is a 3-day old male baby with facial dysmorphisms and was initially suspected to have Patau syndrome. He has midline cleft palate, low set ears, epicanthic folds, and bilateral ear pits with multiple skin tags over both auricles. He also has single palmar creases and micropenis. He is a product of non-consanguineous marriage. There is no family history of dysmorphism. A peripheral blood sample from the baby was sent for cytogenetic analysis and found to be abnormal with a karyotype of 47,XY,+der(22)t(11;22)(q23;q11.2). Fluorescence in-situ hybridisation (FISH) was performed and confirmed the presence of a derivative chromosome 22 comprising of the proximal part of chromosome 22 and the distal part of chromosome 11. These findings are consistent with the diagnosis of Emanuel syndrome. Parental karyotyping revealed that the mother has a balanced translocation (11;22)(q23;q11.2). *Discussion:* Almost all ES patients inherit the derivative chromosome from an unaffected parent. Meiotic 3:1 malsegregation in the carrier parent and subsequent fertilisation with a normal gamete results in a tertiary trisomy zygote, where there is an extra copy of 22pter-22q11.2 and 11q23-11qter.

GP6: The association of iron deficiency and *TMPRSS6* gene polymorphisms among overweight and obese adults

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Introduction: Obesity is becoming a socioeconomic burden in Malaysia and shreds of evidence have linked obesity and iron deficiency (ID) and iron deficiency anaemia (IDA). A strong association between transmembrane protease serine 6 *(TMPRSS6)* gene variants and ID was previously reported among the non-obese population. The influence of *TMPRSS6* genetic variants on the susceptibility to ID among overweight and obese population is unknown. In this study, we evaluated the association between *TMPRSS6* SNP (rs855791, rs4820268 and rs5756504) with haematological indices, iron profiles and inflammatory biomarkers among overweight/obese adults with ID/IDA. *Materials & Methods:* Sixty-two overweight and obese subjects were enrolled in this study. Blood samples were collected and the association of the rs855791, rs4820268 and rs5756504 on haematological indices, iron profiles and inflammatory biomarkers were assessed. *Results:* There was a significant association between rs855791 SNP and the incidence of ID in which the levels of haemoglobin, haematocrit (Hct), mean corpuscular haemoglobin concentration (MCHC), serum iron (SI), transferrin saturation (TS) and hepcidin were found to be significantly reduced in overweight and obese population. Among ID/IDA groups, A/A carriers of rs855791 were significantly associated with reduced Hct and hepcidin levels whereas the G/G carriers of rs5756504 were substantially associated with reduced levels of hepcidin and leptin. *Discussion:* We found that rs855791 in *TMPRSS6* gene was associated with reduced haemoglobin, Hct, MCHC, SI, TS and hepcidin levels consistent with previous studies. We also discovered a significant association between rs5756504 and reduced levels of Hct and hepcidin among this population.

GP7: Genotype analysis of JR blood group and development of amplification refractory mutation system PCR in Korean population

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Introduction: The JR blood group system (ISBT JR 032), which has one antigen, Jr^a, is generally known as a high prevalence antigen in most population. Jr(a-) phenotype has been reported to be relatively higher in Japanese and Asian population. Jr^a antigen is encoded by the ATP-binding cassette, member G2 *(ABCG2)* gene on chromosome 4q22.1. Jr(a-) individuals can be incidentally identified by the production of anti-Jr(a) antibodies and confirmed by the presence of two null alleles of *ABCG2*. The mutation site in *ABCG2* is different according to ethnic group and c.367C>T has usually been found in Asian population. *Materials & Methods:* We have analysed the genotype frequency of *ABCG2* null allele (c.376C>T, rs72552713) from 300 national healthy population cohort using direct sequencing, comparing with calculated frequencies from public genomic databases. Additionally, we developed a simple and robust genotyping method, tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) technique that can be adopted in clinical setting. *Results:* We

found 14 individuals who were heterozygous for *ABCG2* null allele from 300 population cohort. We have optimized the ARMS-PCR assay to detect this null allele and successfully detected the heterozygosity of this null allele in concordance with direct sequencing. *Discussion:* The minor allele frequency of *ABCG2* null allele was 0.023 in Korean and the estimated genotype frequencies of homozygote and heterozygote for this variant allele were 0.05% and 4.56%, which were higher than calculated ones (0.04% and 3.71%) from genomic databases. The newly developed ARMS-PCR assay can make clinical laboratory be prepared for Jr(a-) detection.

GP8: *EGFR* exon 20 insertions in Malaysian non-small cell lung cancer patients: Insights from next-generation sequencing profiling

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Introduction: EGFR exon 20 insertions (ex20ins) have been reported to confer resistance to *EGFR* tyrosine kinase inhibitors. We assessed the prevalence and characteristics of *EGFR* ex20ins in a cohort of Malaysian non-small cell lung cancer (NSCLC) patients. *Materials & Methods:* A total of 303 NSCLC samples underwent next-generation sequencing (NGS) diagnostics at the Subang Jaya Medical Centre, and subsequent descriptive and statistical analyses were conducted. *Results: EGFR* aberrations were detected in 135 (44.6%) patients; mutations (n=118, 38.9%), amplification (2, 0.7%) and mutations with amplification (15, 5%). The most prevalent *EGFR* mutations were the exon 19 deletions (72, 23.8%), followed by L858R (39, 12.9%) and ex20ins (14, 4.6%). Among patients with ex20ins, the median age was 61 years and 57.1% were female. The tumour subtypes were adenocarcinoma (n=11), adenosquamous (2), and squamous cell carcinoma (1). Five patients had co-occurring *EGFR* amplification, 3 harboured *TP53* mutations and 1 had a *CTNNB1* mutation. None of these patients had concomitant driver mutations. Common ex20ins variants were S768_D770dup (n=4) and A763_Y764insFQEA (n=2). One variant is novel and has not been reported in literature. Patients with *EGFR* ex20ins exhibited significantly lower PD-L1 expression (p=0.023) compared to all other cases without *EGFR* ex20ins. *Conclusion:* The *EGFR* ex20ins ranks third in prevalence among *EGFR* mutations in this patient cohort. The location of ex20ins affects drug sensitivity and A763_Y764insFQEA may respond to first and third-generation EGFR inhibitors. Therefore, variant detection and identification by NGS enables precise selection of patients who are likely to benefit from certain targeted therapies.

GP9: A case of combined partial trisomy 3 and partial trisomy 9 foetus derived from maternal balanced translocation t(3;9)

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Introduction: Partial trisomy 3 or partial trisomy 9 may occur de novo due to duplication of a segment of either chromosome or inherited from parental balanced translocation involving either chromosome. Both can result in congenital malformations that can be detected antenatally. *Case report*: A 31-year-old woman was initially referred to the specialist obstetric clinic at 22 weeks of gestation due to intrauterine growth restriction detected during antenatal booking. Detailed ultrasonography done at 29 weeks of gestation revealed congenital diaphragmatic hernia, strawberry-shaped cranium, bilateral ventriculomegaly, hypotelorism, and pseudodextrocardia. Amniotic fluid karyotype showed 47,XX,+mar karyotype pattern in all metaphases. Karyotyping of maternal blood revealed 46,XX,t(3;9)(q29;q31) karyotype pattern which was confirmed by fluorescence in-situ hybridisation, while the father's karyotype is normal 46,XY. The foetus was delivered at 40 weeks and 9 days of gestation and only survived for an hour after delivery. Clinical examination of the baby shows dysmorphic features as follows: prominent parietal bone, fused coronal suture, heart apex on the right side, hepatosplenomegaly, dislocated hip and ambiguous genitalia. *Discussion*: This case of partial trisomy 3 and partial trisomy 9 occurred when the foetus inherited an extra maternally-derived derivative chromosome 3;9. The malformations detected antenatally befits the description of cases of partial trisomy 9 based on previously reported cases, likely due to larger segments of chromosome 9 present in the extra derivative chromosome. To the best of our knowledge, this is the first-ever reported case of combined partial trisomy 3 and partial trisomy 9 with predominant trisomy 9 features.

GP10: Whole exome sequencing revealed a novel *XIAP* mutation in a child with a complex phenotype

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Introduction: Inborn errors of immunity (IEI), previously known as primary immunodeficiencies (PID) refers to a group of genetic defects that leads to immune dysfunction. Diagnosing IEI is challenging in view of polygenic nature of the disease and the lack of genotype-phenotype association for most of the conditions. Hence, next generation sequencing such as whole

exome sequencing (WES) is currently the preferred method to diagnose IEI for its ability to screen many genes simultaneously. In this study, we utilized WES to establish a genetic diagnosis in a child suspected to have IEI. *Case report:* A six-year-old boy was referred for genetic testing using WES. He presented with three episodes of haemophagocytic lymphohistiocytosis between the age of 1 year and 3 years. This was followed by early onset inflammatory bowel disease which is resistant to standard medical therapy. Preliminary immunologic screening showed reduced lymphocyte subsets. WES was performed on Illumina HiSeq 4000 platform. Raw WES data was analysed using in-house bioinformatics pipeline. Variant calling was performed with Genome Analysis Toolkit (GATK). Variants were annotated using web-based ANNOVAR, then were filtered based on the latest update by the International Union of Immunological Societies. Candidate genes were then filtered according to allele frequency and phenotype matching. Whole exome sequencing revealed a novel c.214_217dup (p.73Trp*) mutation in *XIAP*. This variant has not been reported. His asymptomatic mother was detected to be a carrier. *Discussion:* Our report describes a novel mutation in *XIAP* c.214_217dup (p. Trp 73*) which is inherited from a carrier mother.

GP11: Identification of the most common HMGCS2 gene variant in four unrelated Malaysian patients with mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase-2 deficiency

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Introduction: Mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase-2 deficiency (HMGCS2D) is a rare autosomal recessive metabolic disorder caused by mutations in the HMG-CoA synthase-2 (HMGCS2) gene, located on chromosome 1, which consists of 10 exons, leading to ketogenesis disruption. The clinical and laboratory manifestations of HMGCS2D can mimic other metabolic disorders, making definitive diagnosis challenging and often requiring molecular tests. Here, we present our experience identifying HMGCS2 gene variants in Malaysian patients with suspected HMGCS2D. *Materials & Methods:* This retrospective cohort study included 15 samples (6 probands and 9 family members) referred to the Institute for Medical Research from February 2019 to April 2023. Genetic diagnosis involved PCR amplification of all coding regions including splice sites of HMGCS2 gene followed by Sanger sequencing to detect causative mutations. Pathogenicity of variants was confirmed using clinical databases such as VarSome and Franklin in accordance with ACMG guidelines. *Results:* Out of six probands, four had variants suggestive of HMGCS2D with c.1502G>C being the most common variant identified in this study. The variant was predicted to be likely pathogenic by bioinformatics analysis. The other variants were c.182_194del, c.830T>A and c.559+1G>A. *Discussion:* This study highlighted the frequent occurrence of the c.1502G>C variant in unrelated Malaysian patients, suggesting it may be a hotspot mutation. Mutational hotspots are valuable as diagnostic markers, offering cost-effective and time-efficient screening for at-risk family members. Early detection enables timely interventions and preventive measures.

GP12: Chromosome 1q43 deletion syndrome associated with craniofacial dysmorphism: A case report

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Introduction: The chromosome 1q43-q44 deletion syndrome (OMIM® #612337) is a rare chromosomal disorder caused by distal chromosome 1q deletion. This syndrome has been reported in at least 230 cases, and are highly variable in phenotype and severity. Severe cases commonly involve neurodevelopmental anomalies, while milder cases may only manifest with characteristic craniofacial features. The most common neurodevelopmental findings are corpus callosum anomalies, microcephaly, seizures and global developmental delay. To the best of our knowledge, this is the first reported case of 1q43 deletion in a Malaysian child. *Case report:* A 1-month old girl presented with craniofacial dysmorphisms of broad forehead, left eye ptosis, hypertelorism, flattened philtrum, micrognathia and low-set ears. Peripheral blood was sent for conventional cytogenetic analysis which revealed an abnormal chromosome 1 with additional material of unknown origin at 1q terminal region. Subsequently, parental screening showed that the proband's father has an apparently balanced reciprocal translocation between chromosomes 1 and 5 with the karyotype: 46,XY,t(1;5)(q43;q33). The unbalanced derivative chromosome 1 was then passed on to his daughter. The revised karyotype of the child thus read as; 46,XX,der(1)t(1;5)(q43;q33)pat. *Discussion:* Various genes can be involved in this deletion, among which *ZBTB18, AKT3* and *HNRNPU* are associated with corpus callosum anomalies, microcephaly and seizures. At time of writing, the patient is scheduled for further investigations for brain anomalies. Other features may manifest later in life in this patient. Thus, close monitoring of this child is highly recommended for early intervention and treatment.

GP13: Paradigm shift: CNS tumour molecular genetic diagnostic advancement

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Introduction: There are major changes encompassing standardisation of tumour grading and nomenclature as well as increased incorporation of molecular markers in the classification of CNS tumours. The identification of molecular markers can help to determine the diagnosis, prognosis and treatment of CNS tumours. *Materials & Methods:* Total of 115 brain tumours data from January 2021 to Jun 2023 were included in this study. DNA was extracted from FFPE tissue with tumour percentage between 10-40%. *MGMT* and *IDH* mutations were tested using pyrosequencing and RT-PCR respectively. 1p and 19q and *CDKN2A* were analysed using FISH. *Results:* From all glioma cases, 36.5%, 19.1%, 22.6% and 1.7% show positive for *MGMT* methylation, *IDH* mutations, 1p/19q-codeleted and *CDKN2A*, respectively and 20.1% negative for all tested markers. Around 62.5% of *IDH*-mutant astrocytoma were negative 1p/19q, while the remaining 37.5% were positive 1p/19q-codeleted. For glioblastoma, 35.7% positive *MGMT* methylation, 23.8% *IDH*-mutant and 22.6% 1p/19q-codeleted, while 17.9% negative for tested markers. *Discussion:* Astrocytoma *IDH*-mutant is now regarded by WHO as a single tumour type with grades 2, 3 and 4. A 1p/19q-codeleted oligodendroglioma has a more favourable prognosis compared to glioblastoma due to its sensitivity to chemotherapy and radiation. Additionally, glioblastoma is characterized by *IDH*-WT, MGMT gene, which can lead to resistance chemotherapy and respond to alkylating agent. Advances in molecular genetics have resulted in more accurate diagnosis and prognosis of CNS tumours and better management for patients.

5. Haematology

HM1: A case of synchronous chronic myelomonocytic leukemia (CMML) and CD5 negative low grade B-lymphoproliferative disease (LPD)

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Introduction: Haematopoietic stem cells differentiate into myeloid and lymphoid lineages. Most of the haematologic malignancies diagnosed arise from one of these progenitor cells. Rarely do patients present with both a lymphoid and myeloid neoplasm. Herein, we report a case of synchronous diagnosis of both chronic myelomonocytic leukaemia (CMML) and CD5 negative low-grade B-lymphoproliferative disease (LPD). *Case report*: A 83-year-old gentleman with benign prostatic hyperplasia presented with epigastric pain for 2 weeks and loss of weight for 5 months. On examination, his vital signs were normal with evidence of splenomegaly. However, no lymphadenopathy. Full blood count showed mild anaemia (Hb 11.3 g/dl), leucocytosis (white blood cells, WBC, 24.96 x 10^9/L), with absolute monocytosis (AMC 15.70 x 10^9/L) and thrombocytopenia (platelet count 60 x 10^9/L). Peripheral blood smear showed some dysplastic monocytes with occasional promonocytes and blast cells. Bone marrow aspirate revealed hypercellular marrow with evidence of monocytosis, background dysplasia and excess of blasts/promonocytes (12%). Immunophenotyping showed 20% monocytes with 6% blasts/promonocytes. Bone marrow biopsy revealed an increased monocytic component consistent with CMML and synchronous lymphoproliferative infiltrate CD5 negative low-grade B-LPD which differential diagnosis includes lymphoplasmacytic lymphoma and marginal zone lymphoma. Lactate dehydrogenase was also elevated. *Discussion*: A synchronous diagnosis of CMML and lymphomas is a quite rare event. It is probably related to increasing genetic mutation with age for both conditions. The management and treatment of lymphoid neoplasms presenting with concomitant CMML is also challenging, due to the lack of large series.

HM2: Small device, big impact: point-of-care testing for glucose-6-phosphate dehyrogenase (G6PD) deficiency in six Proto Malay Orang Asli settlements

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Introduction: G6PD deficiency (G6PDd) is an X-linked disorder characterized by reduced enzyme activity, leaving red cells vulnerable to oxidative damage and haemolysis. When exposed to triggering factors, G6PD-deficient individuals may develop severe complications such as acute haemolytic anaemia. Point-of-care testing (POCT) is a small but powerful device that can produce rapid quantitative results and make a big impact on healthcare outcomes, particularly in remote communities such as the Proto Malay Orang Asli (PMOA). This paper explored the use of POCT for G6PDd in study of prevalence and mutational spectrum. *Materials & Methods:* A total of 180 blood samples were collected among Orang Asli residing in six settlements on Peninsular Malaysia's west coast. Samples were analysed using Carestart™ S1 (S1) and spectrophotometric assay, OSMMR2000D. Mutational spectrum was analysed using G6PD GenoArray Diagnostic kits. *Results:* A total of 59 males and 121 females were screened for G6PDd. The adjusted male median (AMM) by S1 was 7.0 U/gHb and by OSMMR was 9.2 U/gHb. Reliability analysis showed moderate Pearson's correlation (r=0.61), with a mean difference of 2.3±1.4 U/gHb. The cut off values based on reference assay for severe (<30% AMM) and moderate (<80% AMM) deficiencies were 2.76 U/gHb and 7.36 U/gHb, respectively. The prevalence of G6PDd was 13.3%. Three dominant variants of G6PD

mutations were found; G6PD Coimbra (592C>T)(41.6%), G6PD Viangchan (871G>A) (37.5%), Union (454A>C)(8.3%), and one compound heterozygous case of G6PD Coimbra+Kaiping (592C>T, 1388G>A). *Conclusion:* G6PDd is highly prevalent among the PMOA population and POCT is a suitable tool for quantitative G6PD screening.

HM3: Thalassaemia and haemoglobinopathies screening among Proto Malay Orang Asli community in Peninsular Malaysia

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Introduction: Molecular studies of thalassaemia and haemoglobinopathies in Malaysia are well studied among Malay, Chinese, and Senoi Orang Asli (OA). However, there is no comprehensive study among Proto-Malay OA despite being the second largest OA population comprising six sub-ethnics with resemblance to the modern Malay population. This study aims to screen for thalassaemia and haemoglobinopathies among Proto-Malay specifically Temuan group only to ensure genetic homogeneity. *Materials & Methods:* Study was done on 258 samples of Temuan OA subjects (167 females, 91 males). Full blood count (FBC) analysis was conducted followed by haemoglobin analysis using capillary electrophoresis (CE). Diagnosis was confirmed by multiplex amplification refractory mutation system polymerase chain reaction (MARMS-PCR) and Gap-PCR for common alpha deletions and mutations as well as beta gene mutations. *Results:* A total of 62 thalassaemia cases were detected. Majority are αα/-$\alpha^{3.7}$ (60%) followed by αα/ α^{CS} (19.4%), β^N/β^E (11.3%), $\beta^N/\beta^{IVS\ 2\text{-}654\ C\text{-}T}$ (3.2%), homozygous -$\alpha^{3.7}$ (3.2%), concomitant αα/-$\alpha^{3.7}$ with β^N/β^E (1.6%), and $\alpha\alpha^{CS}$/-$\alpha^{3.7}$ (1.6%). Only 2 cases of beta-thalassaemia traits with IVS 2-654 (C-T) were detected, which is rare in the Malay but commonly found in Chinese ethnicity. Additionally, 26 hypochromic microcytic cases with normal Hb analysis require further advanced molecular testing to attain a diagnosis. *Conclusion:* These findings dictate that thalassaemia and haemoglobinopathy are common in the Proto-Malay population with heterogenous molecular characteristics. The study of molecular spectrum among OA will help in genetic counselling and prenatal screening to reduce the burden of disease and to improve morbidity and mortality outcomes of patients with thalassaemia.

HM4: A correlation study of the platelet count, the percentage of immature platelet fraction and bone marrow thrombopoietic activity

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Introduction: Fully automated flow cytometry has revolutionized the field of blood cell counting, enabling reliable quantification of reticulated platelets and calculation of the immature platelet fraction (IPF). IPF, expressed as a percentage, serves as an indicator of thrombopoiesis, reflecting changes in platelet production rates. Additionally, Platelet-F (PLT-F) has been developed to provide accurate and precise platelet counts, particularly when levels are <50x10^9/L. On the other hand, bone marrow aspiration and trephine biopsy (BMAT) offer information about platelet production, including the number of megakaryocytes. However, these procedures are invasive, time-consuming, and have subjective interpretations, limiting their routine clinical application. *Materials & Methods:* This cross-sectional study was conducted over 12 months in Hospital Melaka which encompassed all cases of bone marrow aspiration sent to Haematology laboratory. The primary objective was to establish a correlation between PLT-F, IPF, and bone marrow thrombopoietic activities. *Results:* The results revealed a significant negative correlation between PLT-F and IPF, indicating that as platelet production increases, the percentage of reticulated platelets decreases, and vice versa. However, the strength of this correlation was found to be weak (r=-0.254). Furthermore, a significant association was observed between PLT-F with both bone marrow and trephine biopsy thrombopoietic activities. Each unit increase in PLT-F corresponded to 0.004 and 0.007 increase in bone marrow and trephine biopsy thrombopoietic values respectively. Conversely, no significant association was found between IPF and neither bone marrow nor trephine biopsy thrombopoietic activities. Additionally, there were no significant mean differences in bone marrow and trephine biopsy results between individuals with haematological and non-haematological malignancies (p=0.156 and p=0.223) respectively. *Discussion:* The inverse correlation between PLT-F and IPF aligns with previous studies, suggesting that IPF reflects the severity of platelet destruction. However, the significance of the correlation between IPF and bone marrow thrombopoietic activity could not be established due to potential unmeasured factors. It is important to note that this study primarily focused on diagnostic and reassessment bone marrow cases related to haematological malignancies rather than hyperdestructive conditions. Consequently, further studies with larger sample size are necessary to determine this correlation conclusively.

HM5: Mutation analysis of *BCR::ABL1* kinase domain in chronic myeloid leukaemia patients with tyrosine kinase inhibitors resistance: A Malaysian cohort study

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Introduction: BCR::ABL1 kinase domain (KD) mutation status is an important element of clinical decision algorithms for chronic myeloid leukaemia (CML) patients who do not achieve optimal response to tyrosine kinase inhibitors (TKIs). Although Sanger sequencing (SS) is considered the gold standard for *BCR::ABL1* KD mutation screening, the use of next-generation sequencing (NGS) has recently been assessed. *Materials & Methods:* In the current study, both SS and NGS were performed for the mutational analysis of *BCR::ABL1* KD in 84 CML patients with TKI resistance and 20 CML patients who achieve deep molecular response (DMR). *Results:* In total, 12 different *BCR::ABL1* KD mutations were identified by SS in 22.6% (19/84) of patients who were resistant to TKI treatment. Interestingly, NGS analysis of the same patient group revealed an additional three different *BCR::ABL1* KD mutations in 27.4% (23/84) of patients. These mutations are A344V, E355A, and E459K with variant read frequency below 15%. On the other hand, in patients who achieved deep molecular response (DMR), NGS identified 5 mutations in 30% (6/20) of patients. However, mutation F317S was missed by SS and thus identified 4 mutations in 25% (5/20) of patients in DMR. *Discussion:* The use of NGS is advised for accurately determining the mutation status of *BCR::ABL1* KD, particularly in cases where the allele frequency is low, and for identifying mutations across multiple exons simultaneously. Therefore, the utilization of NGS as a diagnostic platform for *BCR::ABL1* KD mutation testing is very beneficial to guide therapeutic decision-making.

HM6: Full blood count changes in Coronavirus disease 2019 (COVID-19) patients

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Introduction: COVID-19 infection has been associated with full blood count (FBC) parameter changes which are linked to the severity and prognosis of a patient. This study aimed to identify the changes in the FBC parameters concerning patients' characteristics, the severity of the disease and vaccination status. *Materials and Methods:* A cross-sectional retrospective laboratory analysis involved 208 respondents confirmed positive COVID-19 selected from July to November 2021 in Pathology Department, Hospital Tuanku Ja'afar Seremban, Negeri Sembilan. Patients were further classified into their covid clinical stages, severity, vaccination status and outcome. *Results:* Severe patients had significantly lower absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute eosinophil count (AEC) and absolute basophil count (ABC) but higher mean platelet volume (MPV), absolute neutrophil count (ANC), neutrophil to lymphocyte ratio (NLR) and immature granulocytes (IG) compared to the non-severe patients ($p<0.05$). Non-survivor showed similar findings ($p<0.05$). Fully vaccinated patients had significantly lower NLR and MPV but higher ALC, AMC, AEC and ABC than unvaccinated or partially vaccinated patients($p<0.05$). *Conclusion:* ALC, AMC, AEC, ABC, MPV, ANC, NLR and IG in COVID-19 patients were significantly different when compared to patients' severity, outcome, and vaccination status. These results might give better insight for the clinician to anticipate the severity and outcome of a patient from their full blood count parameters.

HM7: Molecular and flow cytometry characteristics of non-APML, HLA-DR negative and CD34 negative acute myeloid leukaemia (AML)

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Introduction: Non-APML, HLA-DR negative and CD34 negative AML is a different entity from acute promyelocytic leukaemia (APML). The blast immunophenotype is unable to distinguish between the two and it is frequently misdiagnosed and treated as APML. Molecular mutation can differentiate them in which NPM1 is mainly found in the earlier type whereas PML RARA is found in APML. This study aimed to characterize this AML by its immunophenotyping, molecular findings and prognosis compared with APML. *Materials and Methods*: A cross-sectional study was carried out at HSAJB, involving all cases diagnosed as AML for a duration of 3 years. The proportion of APML and non-APML, HLA-DR and CD34 negative AML with their prevalent immunophenotypes, molecular mutations and prognosis were compared. *Results:* A total of 182 AML cases were collected. No statistical significance was found between the two types of AML by immunophenotypes. However, a higher proportion of APML cases expressed CD11c and CD14 negative in comparison to the non-APML cases. Only 69 samples had positive molecular mutations. Eight cases of non-APML, HLA-DR and CD34 negative AML had NPM1 and NPM1 with FLT3 ITD mutations. Non-APML, HLA-DR and CD34 negative AML with NPM1 had a good prognosis. *Conclusion:* A more extensive antibody panel in flow cytometry and a bigger sample size might have a better outcome to distinguish the two types of AML. NPM1 being the prevalent molecular mutation in the non-APML group places this group in the good prognosis category. Advances in molecular testing will be beneficial as more molecular mutations are identified together with NPM1 besides FLT3 ITD.

HM8: Para-Bombay phenotype – A case report of a rare blood group in a tertiary centre

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Introduction: There have been very limited case studies on Para-Bombay individuals as it is a rare phenotype worldwide. They have often been mislabelled as group O. Herein, we reported a case of undetected Para-Bombay A phenotype in a previously known blood group O patient. *Case report:* A 71-years-old lady presented with bleeding right brachiocephalic fistula. Her haemoglobin level was 6.7g/dL and required a packed cell transfusion. Patient had previous ABO blood grouping of O RhD positive in July 2020 and history of multiple uneventful transfusions with O RhD positive packed cell. This admission, an ABO discrepancy was detected in which forward grouping showed O Rh D positive while reverse grouping of blood group A. Further enhancement test was negative. Extended test with anti-H lectin revealed no reaction. This raised the suspicion of a Bombay/Para-Bombay phenotype as opposed to subgroup, which will have stronger reaction with anti-H lectin. O cell revealed negative result with negative antibody screening and no evidence of wide thermal range amplitude of anti-H. Adsorption/elution test showed absence of A, B and H antigen while saliva secretor study revealed presence of A and H substance which confirmed Para-Bombay A. *Discussion:* Para-Bombay phenotype is usually detected as a result of ABO discrepancy and easily missed without extended tests. This case illustrates the importance of resolving ABO discrepancy by using anti-H reagent for blood grouping and supplementary test of adsorption/elution with secretor study. Proper determination of blood group is required prior to transfusion as it is significantly affect transfusion management.

HM9: Just an autofluorescence confusion or a rare case of triple positive acute promyelocytic leukaemia?

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Introduction: Acute promyelocytic leukaemia (APML) with *PML::RARA* is a leukaemia with circulating abnormal promyelocytes of bilobed-nuclei and pathognomonic faggot cells. They are characterised by immunophenotyping (IPT) profile of CD117 with low/absent HLA-DR and CD34. These findings are often used to guide the initiation of all-trans-retinoic acid (ATRA) before confirmatory molecular and cytogenetics results are available. *Case report:* A 34-year-old female, presented with menorrhagia for one week. Investigations showed severe pancytopenia with 20% of abnormal promyelocytes and presence of faggot cells. An urgent peripheral blood IPT was performed and showed 43% abnormal promyelocytes with the following expression: CD45 dim/ moderate-high side-scatter/ CD34+/CD117+/HLADR+/ cyMPO+/CD13+/CD33+/CD64+/CD16-, which are uncommon for APML. Repeated IPT using unstained sample demonstrated increased fluorescent signals for at least one log, across all channels. Particularly, CD34-PercCP-Cy5.5 signal intensities are similar for both stained and unstained samples. It is likely that autofluorescence from the abnormal promyelocytes cause false positivity of CD34 and possible HLA-DR to certain degree. Cytogenetics and molecular studies had later confirmed the underlying t(15;17) and *PML::RARA* (BCR1) fusion transcript. *Discussion:* Autofluorescence are light signals, emitted by unstained, illuminated cells, a well-known source of interference in flow cytometry. A study showed that APML cells had significantly higher autofluorescence than other AML cases. There are only 9% of APML cases with immunophenotype resembling myeloblasts with triple CD117, CD34 and HLA-DR positivity. APML is a haematological emergency, and timely initiation of ATRA is life-saving. Morphological findings shall remain as gold standard for diagnosis in the event of atypical IPT profile.

HM10: We are not the same! A case report of discordant lymphoma from a single referral centre in Malaysia

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Introduction: Discordant lymphoma is the coexistence of two distinct histologic subtypes of lymphomas in at least two separate anatomic sites. Currently, limited studies of reported cases resulting in true prevalence and clinical outcomes remained obscured. Thus, limited consensus available for optimal management strategies. *Case report*: We report a case of a 65-year-old man who presented with epigastric discomfort and constipation for 6 months. Full blood count shows Hb 13.3 g/dL, WBC $9.1x10^9$, Platelet $231x10^9$, ANC $6.3x10^9$, ALC $2.6x10^9$ and full blood picture shows no leucoerythroblastic picture or abnormal lymphoid cells. However, serum lactate dehydrogenase is elevated, 282 U/L. CT scan identified large left enhancing and homogenous retroperitoneal mass on left perinephric region. Biopsy of retroperitoneal mass was revealed Diffuse Large B Cell Lymphoma (DLBCL). Bone marrow aspirate and trephine biopsy done noted to have low grade B-lymphoproliferative disease with differential diagnosis of marginal zone lymphoma (MZL) or lymphoplasmacytic lymphoma (LPL). He is treated as aggressive lymphoma with RCHOP chemotherapy and currently completed first cycle uneventful. *Discussion*: Discordant lymphoma of indolent histologic subtypes in bone marrow confers a good prognostication and overall survival compared to the concordant lymphoma of aggressive lymphomatous subtypes. In fact, some studies reported that survival rates of indolent discordant lymphoma are similar to cases without lymphomatous bone marrow infiltration of concordant aggressive lymphoma. *Conclusion*: Despite the advancement of PET-CT scan, histopathological evaluation plays an important aspect in the staging purpose of lymphoma as highlighted by this case.

HM11: Identification of Philadelphia Chromosome-like B-cell Acute Lymphoblastic Leukaemia in adults: A single centre experience

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Introduction: Acute Lymphoblastic Leukaemia (ALL) is an aggressive form of haematological malignancy. Unlike B-ALL in children where cure rate is around 80-90% via intensive chemotherapy, adults with B-ALL suffer from relapse with poor overall survival in up to 40% of patients. In order to effectively risk-stratify patients for prognostication, all adult ALL patients were screened for the presence of the recurrent translocation, Philadelphia (Ph) chromosome where targeted therapy is administered in combination with chemotherapy to improve their outcome. However, this strategy does not account for the poor outcomes seen in Ph-negative ALL patients. Within Ph-negative is a newly identified high-risk entity called Ph-like B-ALL. To date, there are no studies actively investigating the genomic landscape of Ph-like B-ALL in the Malaysian population. Therefore, in this study we aimed to identify the genetic aberrations in adults with Ph-negative B-ALL. *Materials & Methods:* In Hospital Ampang, the largest Haematology Referral Centre in Malaysia, a total of 46 diagnostic samples of adult patients with Ph-negative B-ALL were screened for 20 common rearrangements for *CRLF2, ABL*-class and *JAK2* in the current literature by using multiplex PCR reactions. *Results:* Forty-three (93.5%) were negative while 3/46 or 6.5% harboured the *CRLF2* rearrangement. *Discussion:* There is significant lack in information on the human transcriptome related to its overall risk and prognosis that would improve our understanding of its biology to support or recommend any management options. These findings serve as the foundation towards development of a customised mutational analysis panel to be used at diagnosis.

HM12: Association of elevated D-Dimer levels with disease severity and pulmonary embolism in COVID-19: Retrospective analysis and predictive value

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Introduction: COVID-19 patients with high D-dimer levels are at increased risk of severe disease and poor outcomes. Pulmonary embolism (PE), a common complication of COVID-19, further elevates D-dimer levels, necessitating increased D-dimer testing in COVID-19 cases. *Materials & Methods:* A retrospective analysis was conducted on 196 COVID-19 patients hospitalized at Hospital Selayang between June and September 2021, by examining demographic data, laboratory results, and radiological characteristics of CT pulmonary angiography. Ninety-six patients (49%) with positive PE had significantly higher median D-dimer levels (2.86 mg/dL; IQR: 7.91) compared to those without PE (1.15 mg/dL; IQR: 1.10). D-dimer levels were significantly associated with disease severity (area under the ROC curve of 0.777; CI: 0.660, 0.895; *P*: 0.013). The Youden index was used to determine a cutoff value of 2.10 mg/mL for predicting PE. The univariable logistic regression model showed a sensitivity of 60.4% and a specificity of 79% in predicting PE (95% CI: 50.5, 69.8 [true positive rate, 58 out of 96]) and a specificity of 79% (95% CI: 70, 86 [true negative rate, 79 out of 100]). The regression model exhibited an area under the ROC curve of 0.72 (95% CI: 0.649-0.795). Various cutoff values at 0.5, 0.8, 1, and 1.5 mg/dL revealed that higher D-dimer cutoffs increased specificity but decreased sensitivity. *Conclusion:* This study emphasizes the predictive value of D-dimer in assessing the severity of COVID-19. Higher D-dimer cutoff values may help reduce unnecessary pulmonary CT angiography scans, thus optimizing resource utilization.

HM13: The challenges of running a local external quality assurance (EQA) programme

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In January 2013, the College of Pathologists, Academy of Medicine of Malaysia registered a limited company called MCPath QAP (Malaysian College of Pathologists Quality Assurance Programmes) to offer external quality assurance programmes for diagnostic laboratories. This poster introduces the broad range of quality assurance programmes in all disciplines of pathology to serve the medical and scientific communities in Malaysia. We also highlight the challenges in running the local EQA programme; and compare that of with the challenges faced by the International Academy of Pathology, Malaysian Division who is also running an EQA for their general diagnostic histopathology. This poster drafts the possible future direction of this local effort of external quality assurance programmes.

HM14: Chronic myelomonocytic leukaemia associated with acquired pure red cell aplasia: A case report

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Introduction: The myelodysplastic (MDS) and myeloproliferative neoplasm (MPN) overlap syndromes has markedly a heterogenous clinical phenotype. Chronic myelomonocytic leukaemia (CMML) is the most common subtype in this group. *Case report:* A 59-year-old male who was previously well presented with worsening symptomatic anaemia in the last 5 months. He was severely anaemic and required multiple blood transfusions. No apparent blood loss, haemolytic or infective cause could be elicited. Constitutional symptoms were also absent. Upon admission he was extremely pale but not jaundiced.

He required oxygen via nasal prong though vital signs remained stable. Physical examination was otherwise unremarkable. Hb was markedly reduced at 5.3 g/dL, WBC was elevated with absolute monocytosis and thrombocytopenia. DCT was positive. Peripheral smear showed leukocytosis with left-shifted myelopoiesis and prominent monocytes. Bone marrow examination showed granulocytic hyperplasia and increase in monocytes. Blasts cells were not increased. Megakaryocytes showed prominent features of dysplasia. Interestingly, the erythroid series were absent. *BCR::ABL1* fusion transcript was not detected. A diagnosis of CMML-1 with secondary acquired pure red cell aplasia (aPRCA) was made. He was counselled for hypomethylating agents and allogeneic stem cell transplantation. *Discussion:* CMML is characterized by the proliferation of bone marrow precursors resulting in peripheral monocytosis, as well as underlying dysplasia with a tendency to transform to acute myeloid leukaemia. In the context of a deranged immunological environment, systemic autoimmune and inflammatory diseases may arise. Idiopathic aPRCA is a rare entity that is mediated by selective targeting of erythroid precursors by autoreactive immune effector cells.

HM15: The immunofluorescent test detection of *MYH9* gene associated mutation for platelet disorders in Malaysia

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Introduction: Myosin heavy chain 9 (MYH9)-related platelet disorders (MYH9-RD) belong to the group of inherited thrombocytopenias. The *MYH9* gene encodes the non-muscle myosin heavy chain IIA (NMMHC-IIA), a cytoskeletal contractile protein. Pathogenic *MYH9* variants cause NMMHC-IIA aggregation in neutrophils. Blood smear immunofluorescence detecting the abnormal protein aggregates is a sensitive and specific screening tool used to validate variant pathogenicity. This study was conducted to evaluate the potential of immunofluorescent test screening for suspected MYH9-RD in Malaysia when genetic testing is not available. *Materials and Methods:* A prospective study were conducted on 32 patients with chronic and refractory immune thrombocytopenia using immunofluorescent testing. Presence of abnormal aggregates of NMMHC-IIA indicates positive immunofluorescent test. *Results:* Out of 32 patients, 3 (9.4%) patients had a positive immunofluorescent test, 2 with Type II inclusions and 1 with Type III inclusions. They all had moderate thrombocytopenia with unrecordable mean platelet volume (MPV) indicating platelet anisocytosis. One patient showed inclusion like bodies in the full blood picture. Two of the cases had family history of ITP/easy bruising. Full physical examination showed no other haematological and clinical manifestation. *Discussion:* The abnormal NMMHC-IIA aggregates can be detected via immunofluorescent test. Screening for MYH9-RD using this relatively simple approach is useful when genetic testing is not easily available. Identifying patients with MYH9-RD is important to give them a correct diagnosis and prevent unnecessary/harmful treatments such as steroids and splenectomy in cases of suspected autoimmune thrombocytopenia. Further testing would be required to confirm the genetic origin of this condition.

HM16: Case series of hepatosplenic T cell lymphoma: A rare and aggressive disease

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Introduction: Hepatosplenic T cell lymphoma (HSTCL) is a rare form of T-cell lymphoma that predominantly emerges from neoplastic proliferation of cytotoxic T-cells of γ/δ T-cell receptor-expressing lymphocytes. Its rarity and lack of lymph node involvement causes significant difficulty in diagnosis, which inevitably delays the initiation of treatment. Here, we highlight the clinicopathological features and management of HSTCL over a 10-year span in a single haematology referral center and review of the literature. *Case report:* Six cases of HSTCL were identified. Patients age ranged from 14 to 65 years. Clinical presentation includes hepatosplenomegaly, constitutional symptoms, cytopenias and bone marrow involvement. The neoplastic lymphocytes were positive for pan-T-cell markers but negative for CD4 and/or CD8. Most tested positive for TIA-1 and negative for Granzyme B, consistent with a non-activated cytotoxic T-cell phenotype. γδTCR was positive in half of the cases. For whom cytogenetic studies were performed, i(7q) was detected. Various chemotherapeutic regimens were used. The median overall survival (OS) was 5 (range 1.5-22) months. *Discussion:* Peak incidence occurs in adolescents and young adults, typically presenting with pancytopenia and hepatosplenomegaly. HSTCL mimics various other illnesses. Flowcytometry is the main mode of diagnosis because patients are often ill, limiting the ability to obtain sufficient tissue sampling. Next-generation sequencing has been used to identify actionable recurrent genetic alterations. However, many targeted therapies require evaluation in clinical trials. To date, there is no standard recommendation for chemotherapy in this rare and aggressive lymphoma. Regardless of the treatment modality, the median OS is short at 6-28.3 months.

HM17: Chronic myeloid leukaemia in megakaryocytic blast crisis

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Introduction: Chronic myeloid leukaemia (CML), characterised by the translocation between chromosome 9(9q34.1) and 22(22q11.2), is a triphasic disease that typically progresses through three phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP). Majority of the patients are in the CP, 10% in the AP, and 10% in the BP. Most cases of CML can progress from CP to BP (directly or via AP) within 3-5 years after diagnosis if without effective therapy. In most BP cases, the blast lineage is myeloid (70%) and may include neutrophilic, monocytic, megakaryocytic, basophilic, eosinophilic, or erythroid blasts. The BP of CML with megakaryocytic phenotype is extremely uncommon, accounting for only <3% of all transformed cases. We present a rare case report from 33 years old man who presented with intermittent fever and mild splenomegaly. Morphological and flow cytometry (FCM) assessment showing features of Acute Megakaryocytic Leukaemia (AML, M7). Cytogenetic studies reveal translocation t(9;22) (q34.1;q11.2) that contains the breakpoint cluster region-Abelson 1(*BCR::ABL1*) fusion gene detected by a polymerase chain reaction (PCR). *Discussion*: It is critical to get this case diagnosed correctly since they can benefit from conventional chemotherapy with Tyrosine Kinase Inhibitor (TKI), which lowers the mortality rate.

HM18: Determination of zygosity for Xmn1 polymorphism by next-generation sequencing (NGS) assay

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Introduction: The *Xmn1* polymorphism is a genetic modifier caused by nucleotide changes (C>T) at -158 of the *HBG2* promoter region. The zygosity of the polymorphism is known to correlate with the severity of beta thalassaemia intermedia by increasing the production of Hb F. We use the Devyser NGS assay to detect the polymorphism; however, the cut-off point for variant allele frequency (VAF)% used to discriminate the zygosity is yet to be validated. *Materials & Methods:* The VAF% for 30 cases was retrieved from the Amplicon Suite software system following the detection of the Xmn1 polymorphism by NGS assay. Generally, heterozygous loci are less than 50% VAF, while homozygous loci are more than 50% VAF. To confirm the zygosity, all results were validated using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). *Result:* The VAF% range for the 30 cases was between 21.9 and 56.0%. Eighteen and twelve cases were found to be heterozygous and homozygous, respectively, by PCR-RFLP. The VAF% for heterozygotes was < 41.49% and > 46.41% for homozygotes. No cases with VAF% values between 41.49 and 46.41% were observed. *Conclusion:* The zygosity of the *Xmn1* polymorphism can be reported directly from the NGS assay without secondary validation for cases with a VAF% value of < 41.49% (heterozygous) and > 46.41% (homozygous). Values within the VAF% range of 41.49–46.41% are considered indeterminate and require confirmation. This study showed that zygosity confirmation of the *Xmn1* polymorphism can be done selectively, thus reducing costs and laboratory turnaround times.

HM19: Characteristics of chronic myeloid leukaemia patients with atypical pattern of *BCR::ABL1* rearrangement: A case series from a single referral centre in Malaysia

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Introduction: Chronic Myeloid Leukaemia (CML) is characterized by chromosomal translocation t(9;22)(q34.1;q11.2), giving rise to Philadelphia (Ph) chromosome and results in *BCR::ABL1* fusion gene. Fluorescence in situ hybridization (FISH) not only can confirm *BCR::ABL1* fusion gene, but also detect atypical pattern of *BCR::ABL1* rearrangement. *Case Report:* We present two CML cases with atypical pattern of *BCR::ABL1* with description on patients' clinicopathological characteristics, cytogenetic and molecular response to frontline tyrosine kinase inhibitor (TKI). Both patients had atypical pattern of *BCR::ABL1* detected at diagnosis. Patient 1 had derivative chromosome 9 deletion, while patient 2 had *BCR::ABL1* fusion with ABL1 and BCR deletion. Patient 1 failed to achieve major molecular remission at the most recent follow up. Patient 2 required switching from imatinib to nilotinib due to loss of complete cytogenetic remission. *Discussion:* The *BCR::ABL1* deletion in derivative chromosome 9 is likely due to loss of one or more tumour suppressor genes in some CML patients with large deletions near to the ABL breakpoint. Whereas the BCR deletion of derivative chromosome 22 may be associated with abnormal cell growth and proliferative due to inhibitory effect exerted by binding of GTP-ase-activating protein to $p21^{rac}$. Amongst all atypical pattern of *BCR::ABL1*, derivative 9 deletion may contribute to disease progression. *Conclusion:* Atypical pattern of *BCR::ABL1* rearrangement can be a useful cytogenetic information to help identify chronic myeloid leukaemia (CML) at risk of lower haematological response rates and major cytogenetic response or frontline TKIs treatment resistance.

HM20: A platelet count discrepancy in severe malaria patient

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Introduction: Malaria is a life-threatening mosquito-borne disease in Malaysia. One of the significant manifestations associated with severe malaria is thrombocytopenia. We reported a severe malaria case with platelet count discrepancy by Sysmex XN analyzer. *Case report:* We present a case of a 69-year-old gentleman presented with fever, reduced oral intake and constipation with history of travel to the forest area. Initial full blood count (FBC) done at the Emergency Department (ED) showed that the patient's platelet count was 18,000/μL, while the peripheral blood film (PBF) sample that was sent to the laboratory showed platelet count was 22,000/μL. Manual platelet counting on PBF review showed less than 5 platelets per high power field (HPF) with numerous malaria parasites seen within intact red blood cells (RBC). Repeated FBC on the next day noted platelet count was 345,000/μL and 503,000/μL at ED and laboratory respectively. In view of platelet count discrepancy, another PBF was done using repeated FBC sample, revealing numerous free lying malaria parasites as most of the RBC already ruptured. Manual platelet count remained less than 5 platelets per HPF. We concluded that spurious high platelet count was due to free lying malaria parasite and ruptured RBC that was counted as platelet by analyser. *Discussion:* Platelet counts using impedance analysis method has its limitation in distinguishing platelets from fragmented red blood cells or malaria parasites. This case emphasised the importance of understanding the platelet discrepancy in malaria patients and early recognition of this phenomenon could improve risk stratification and clinical management.

HM21: Classic Hodgkin lymphoma infiltration in bone marrow presenting with autoimmune haemolytic anaemia: A case report

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Introduction: Hodgkin lymphomas (HLs) are lymphoid neoplasms, commonly developed in lymph nodes and it encompasses 90% of classic Hodgkin lymphoma (CHL). HLs involving bone marrow with the presentation of Autoimmune Haemolytic Anaemia (AIHA) is a rare phenomenon, especially in the paediatrics population. We present a case of AIHA at the time of diagnosis of CHL with bone marrow involvement. *Case report:* A 8-year-old boy presented with symptomatic AIHA and neck swelling for two years. Physical examination revealed multiple cervical lymphadenopathy and hepatosplenomegaly. Laboratory investigation showed severe anaemia (Hb 4.4 g/dL), reticulocytosis (20.67%), raised bilirubin and LDH with positive Coombs test. FBP was suggestive of acute haemolysis. Lymph node biopsy was reported as Lymphocyte Rich CHL. Bone marrow aspirate (BMA) demonstrated a normocellular marrow with erythroid hyperplasia and the presence of a suspicious, large, binucleated cell possibly Reed-Sternberg cell. Bone marrow biopsy displayed infiltration by scattered Reed-Sternberg cells and mononuclear Hodgkin cells. These cells stained positive for CD30 and CD15. The patient is currently being treated with the EuroNet-PHL1 treatment protocol, starting with OEPA regime chemotherapy. *Discussion:* The presence of CD30 and CD15-positive Hodgkin and Reed-Sternberg (HRS) cells in an inflammatory background confirmed the marrow infiltration. The scarcity of HRS cells observed in BMA may be due to fibrosis, which is a common finding in HL. Detection of marrow infiltration is crucial as it indicates vascular dissemination and poorer prognosis. The majority of AIHA-associated HL presents in the advanced stage of the disease with haemolysis being the presenting symptom as seen in this case, thus a necessity to exclude HL in patients with AIHA without an obvious cause.

HM22: Dengue fever mimicking plasma cell leukaemia

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Introduction: Circulating extreme plasmacytosis in peripheral blood is an uncommon finding and usually associated with plasma cell leukaemia but rarely with other malignancies, infectious diseases, autoimmune disorders or drug reactions. *Case Report:* We report a 13-year-old girl who had fever, myalgia, arthralgia and vomiting for 3 days. Physical examination was unremarkable. Investigation revealed thrombocytopenia (44 x 10^9/L) and leukopenia (2.9 x 10^9/L) but normal haemoglobin level. Liver enzymes were elevated. Though the initial dengue combo test was negative, she was treated as dengue fever in compensated shock with transaminitis and starvation ketosis. She had an isolated prolonged APTT and low fibrinogen but no bleeding tendency. Her peripheral blood smear showed 22% plasma cells, 21% lymphoplasmacytic lymphocytes, 36% neutrophils, 18% lymphocytes and 4% monocytes while 8-colour flow cytometry of the peripheral blood revealed 16% polyclonal plasma cells. A bone marrow examination was not done. During her 4 days of admission, her symptoms and haematological parameters improved dramatically. Dengue immunoglobulin M was positive on day 5 of illness, consistent with a secondary dengue infection of unknown serotype. Serum paraprotein and free light chain were normal. Her coagulation profiles normalized prior to discharge. *Discussion:* Atypical lymphocytosis is common in dengue fever while transient plasmacytosis is not frequently seen. A recent study showed that plasmacytosis was most pronounced during the first week of disease and disappeared completely within 2 weeks. In patients from dengue-endemic areas, plasmacytosis should be investigated to determine whether transient and related to an acute illness before proceeding to an extensive and intrusive evaluation.

HM23: The unusual compound heterozygous β-haemoglobin variant

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Introduction: Hb Richmond, (NG_000007.3:g.71033C>G) is a rare β-haemoglobin variant, occurs due to amino acid substitution at codon 102 (AAC>AAG) and Poly A mutation occurs at polyadenylation signal site. Diagnosis of haemoglobin variants can be challenging. It may share a similar pattern with other types of thalassaemia. Here we describe a rare compound heterozygous Hb Richmond and Poly A mutation which present with mild clinical phenotype. *Case report:* 1-year-old boy, referred to paediatrician for family screening. Her mother was suspected to have haemoglobinopathy from haemoglobin analysis done in 2012, but she defaulted. Otherwise, the patient is well. On examination, no hepatomegaly. His red cells indices were; haemoglobin 10.3g/dL, red cell count 4.82 $x10^{12}$/L, mean cell volume 66.0 fL and mean cell haemoglobin 21.4 pg. Haemoglobin analysis by capillary electrophoresis (CE) shows an abnormal peak at zone 7 (64.1%) with raised HbA2 (4.5%). High Performance Liquid chromatography (HPLC) shows an abnormal peak at S-window (49.4%) with raised HbA2 (14.6%) and HbF (4.5%). DNA analysis by Sanger sequencing identified compound heterozygous state of Codon 102 [AAC>AAG] Hb Richmond and Poly A [AATAAA>AATAGA] mutations. Family screening identified that Poly-A β-thalassaemia mutation and Hb-Richmond haemoglobin variant was paternal and maternal inheritance, respectively. *Discussion:* Hb analysis for Hb Richmond shares a similar pattern with Hb Q-Thailand, which shows peak at zone 7 in CE and peak at S-window in HPLC. Even though we can suspect it was not Hb Q-Thailand, based on the lower percentage of Hb variant seen in alpha-thalassaemia, gene sequencing plays an important role in identifying the type of haemoglobin variant.

HM24: An exceptionally unusual case of composite tumour of diffuse large B-cell lymphoma and plasma cell myeloma (IgM type) in a bone marrow

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Introduction: The IgM form of plasma cell myeloma (PCM) is very rare and poses a diagnostic challenge. Here, we provide a case study of a patient who had a composite tumour made up of PCM (IgM type) and diffuse large B-cell lymphoma (DLBCL). *Case report*: A 66-year-old man who initially presented with warm autoimmune haemolytic anaemia was later found to have DLBCL and reactive plasmacytosis from the bone marrow. The first reassessment marrow revealed no signs of residual disease but persistent reactive plasmacytosis. He returned six months later with severe anaemia. The repeat bone marrow trephine biopsy showed an increased population of clonal plasma cells with kappa light chain restriction. IgM kappa paraproteinemia with significant immunoparesis was detected by serum electrophoresis, and an ill-defined lytic lesion on L3/L4 was noted from the CT scan. Thus, a diagnosis of PCM (IgM type) was made with no residual malignant DLBCL cells. However, treatment for myeloma was not initiated. The patient was admitted again six months later for severe anaemia (Hb 6.8 g/dL) and weight loss. The full blood picture showed mild rouleaux formation. A repeat trephine biopsy showed two distinct populations consisting of DLBCL and PCM, which was later confirmed by dual immunohistochemistry (IHC) staining of CD138+/CD20- and CD20+/CD138-. *Discussion*: This case illustrates the challenges of diagnostic interpretation with limited diagnostic modalities in distinguishing the two co-existing malignant populations. A high index of suspicion is crucial in deciding on further investigations to ascertain the diagnosis, as this has a major impact on patient treatment and management.

HM25: A retrospective case report of acute myeloid leukaemia with haemophagocytic lymphohistiocytosis from a single referral centre in Malaysia

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Introduction: Haemophagocytic lymphohistiocytosis (HLH) is an immune-mediated life-threatening disease with confusing clinical manifestations. Malignancy-associated HLH in adults is rare, largely under-diagnosed, and our current knowledge relies on case reports and series. *Case report*: We report a case of 69-year-old man with underlying beta-thalassaemia trait and smear-positive pulmonary tuberculosis. He presented with reduced effort tolerance, chest pain, shortness of breath, and fever. He had pancytopenia with Hb 5.8g/dL, WBC 5.7x10^9/L, platelets 20x10^9/L, ANC 0.2 x10^9/L, elevated serum ferritin 909.70x10U/L, AST 89U/L, LDH 853U/L, and CRP 15.90x10^3/dL. Peripheral blood film showed a leukoerythroblastic picture with 83% blast cells. Bone marrow appeared hyper-cellular with 80% myeloblasts accompanied by histiocytes with haemophagocytosis. Immunophenotyping was consistent with acute myeloid leukaemia (AML). Physical examination and chest radiography revealed right upper lobe consolidation. He was diagnosed with severe sepsis secondary to pneumonia with AML. His condition worsened with multi-organ failure, and he later succumbed to death within ten days. Retrospectively, we noted that the patient fulfilled ≥ 5 of the Modified 2009 HLH criteria. Three clinical criteria: fever ≥38.5°C, peripheral blood pancytopenia, and hepatitis. Two immune markers: serum ferritin >500ng/mL and haemophagocytosis in the bone marrow. *Discussion:* Malignancy-associated HLH typically presents with non-specific symptoms that overlap with sepsis, systemic inflammatory response syndrome (SIRS), multi-organ failure, and haematological malignancies. This case represents the need for laborious diagnostic approach, timely manner of identifying HLH, the possibility of multiple triggers (AML and pulmonary tuberculosis infections), and the rapid progression of the HLH process.

HM26: Acanthocytosis associated with suspected myelodysplastic syndrome/pure erythroid leukaemia: A rare presentation

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Introduction: Acanthocytosis isa characteristic of red blood cells associated with various inherited conditions like abetalipoproteinemia or acquired causes related to fat malabsorption. Rarely acanthocytosis has been reported as an indicator of haematological disorders such as myelodysplastic syndrome (MDS). *Case Report:* We herein report an interesting case of acanthocytosis of unknown aetiology in a 77-year-old man with underlying atrial fibrillation (AF), diabetes mellitus and hypertension. He presented with a two weeks history of diarrhoea and had mild hepatomegaly. He was not jaundice and had no splenomegaly palpable. Full blood count (FBC) showed bicytopenia (normochromic normocytic anaemia: haemoglobin level of 77 g/L, reticulocytopenia: 0.41% and thrombocytopenia:platelet: 46 x 10^9/L) with normal white cell count. Retrospectively, his FBC was normal six months prior to this admission. Full blood picture showed marked acanthocytosis, true thrombocytopenia and a very occasional suspicious cell. Renal and liver profiles were both normal, while serum folate was low. Patient was not responding to the folate and intravenous cyanocobalamin challenge. Bone marrow aspiration sample was suboptimal. However, trephine biopsy discovered an excess of blasts, evidenced by marked expansion of erythroid precursors and an increase in blasts/proerythroblasts expressing CD34, CD117, E-cadherin and Glycophorin A. Differential diagnosis include MDS with excess of blasts/ pure erythroid leukaemia. Unfortunately, he succumbed to his illness during the same admission. *Discussion:* This observation aimed to highlight that unexplained acanthocytosis in peripheral blood film may be an important sign of an unrecognized haematological malignancy. Relevant clinical history and supporting laboratory investigations were crucial in establishing a definitive diagnosis.

HM27: Neonatal leukemoid reaction in a preterm infant: A diagnostic dilemma

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Introduction: A leukemoid reaction is defined as a leukocyte count greater than 50,000/μL, mimicking leukaemia, resulting from reactive causes outside the bone marrow. This condition is not uncommon in the neonatal intensive care unit (NICU) population, which can be concerning and requires prompt diagnosis and appropriate management. We report a case of transient leukemoid reaction in a premature newborn. *Case Report:* A female newborn was delivered at a gestation age of 28 weeks, admitted to the NICU due to respiratory distress. The mother was treated for subclinical chorioamnionitis and received two doses of antenatal steroids. On examination, there was no hepatosplenomegaly. Initial investigations revealed the following: Hb 13.3 g/dL, WBC 43,200/uL, PLT 376,000/uL. WBC counts increased to 57,500/uL on the third day of life. Peripheral blood film revealed hyperleukocytosis with the presence of immature myeloid cells and occasional blasts. Blood and ear cultures did not yield any organisms. Lumbar puncture, bone marrow aspiration, and karyotyping were not done. The WBC counts were monitored which showed a gradual reduction. The patient responded well to supportive care. *Discussion:* There are several possible causes for neonatal leukemoid reaction such as antenatal steroid usage, chorioamnionitis, prematurity, severe anaemia, perinatal infection, etc., and our patient has two of these. It has been associated with multiple comorbidities including long-term ventilator support, bronchopulmonary dysplasia, intraventricular haemorrhage, sepsis, and a high mortality rate. Diagnosing leukemoid reactions can be challenging. A careful and comprehensive evaluation is crucial to rule out sepsis, congenital leukaemia, and transient myeloproliferative disorders.

HM28: A rare case of CD5 positive diffuse large B-cell lymphoma with leukaemic presentation: A case report from a single referral centre in Malaysia

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*Introduction***:** Diffuse large B-cell lymphoma (DLBCL) constitutes up to 40% of all non-Hodgkin lymphoma (NHL) cases. Although it may exhibit a myriad of clinical behaviours, leukemic presentation is rare with limited literature available. *Case Report:* We report a case of a 70-year-old gentleman who presented with dyspnoea, B-symptoms and hepatosplenomegaly for 3 weeks. Full blood count shows Hb: 9.3g/dL, WBC: 75.1x10^9/L, Platelet: 49x10^9/L, ANC: 10x10^9/L and ALC: 11.5x10^9/L. Peripheral blood film shows presence of abnormal lymphoid cells and numerous smudge cells. The abnormal lymphoids are pleomorphic, medium to large in size, scanty to moderate amount, pale to basophilic cytoplasm and diffuse chromatin with prominent nucleoli. Bone marrow aspirate flowcytometry showed abnormal cells, positive for CD20, CD19, CD5 and negative for CD10 and CD34. Trephine biopsy confirmed infiltration by CD5 positive DLBCL, ABC-subtype. Unfortunately, he succumbed before chemotherapy treatment. *Discussion:* CD5 positive DLBCL is rare, occurring only in 5-10% of cases. The exact incidence of leukaemic DLBCL is still unknown. To our knowledge, only one case of leukemic CD5+ DLBCL has been reported. Due to paucity of data on the subject, it is unclear whether leukaemic presentation carries a significant prognostic impact. In one study of case series, leukaemic DLBCL is associated with extra nodal involvement and high IPI-score. However, the overall survival appears to be comparable to non-leukaemic DLBCL with high IPI-score receiving R-CHOP. De novo CD5+ DLBCL is often associated with high IPI-score, mainly in Asian countries, and is usually of ABC-subtype. As in this case, the poor prognosis could be attributed to the CD5 positivity, high IPI-score and ABC-subtype.

HM29: Erythrophagocytosis in peripheral blood smear of patient with *Mycoplasma pneumoniae* infection

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Introduction: Erythrophagocytosis by neutrophils is a rare morphological phenomenon that has been described in patients with some haemolytic conditions, including paroxysmal cold haemoglobinuria (PCH). PCH is a rare disorder however it is one of the common causes of autoimmune haemolytic anaemia in children. We report a young girl suffering from cold autoimmune haemolytic anaemia presented with blood neutrophils showing phagocytosed erythrocytes in the cytoplasm. *Case Report:* A 6-year-old girl was presented to hospital with a history of generalised yellowish discolouration over the body associated with cough, tea coloured urine, and fever. Physical examination revealed pallor and jaundice. Laboratory studies showed haemoglobin level of 3.5 g/dL, reticulocyte response 3.40 %, indirect bilirubin 140 umol/L, direct Coombs test (C3d) and *Mycoplasma pneumoniae* antibody were both positive. Peripheral blood smear revealed marked red blood cell (RBC) agglutination with florid erythrophagocytosis by neutrophils and monocytes. She was transfused with packed cells and treated with IV C penicillin, syrup azithromycin and oral prednisolone. She responded well to treatment and was discharged on the day eight of admission with haemoglobin of 9.5 g/dL. *Discussion:* Erythrophagocytosis by neutrophils is most strongly associated with PCH. PCH is caused by an immunoglobulin G antibody that sensitises RBCs at cold temperature by fixing complement to the RBCs, which causes intravascular haemolysis on rewarming. It normally manifests as a transient haemolytic anaemia in young children who have had antecedent infection. In the present case, it is believed that *Mycoplasma pneumoniae* infection is the cause of PCH however Donath-Landsteiner test was not done to support the diagnosis.

HM30: Acquired platelet dysfunction with eosinophilia: A case report

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Introduction: Acquired platelet dysfunction with eosinophilia (APDE) is a rare, acquired benign, transient bleeding disorder associated with eosinophilia and platelet dysfunction. It is mainly reported in South East Asia, affecting mainly patients in the paediatric age group. Helminthic infestation has been associated in about 50% of cases. *Case Report:* An 11-year-old boy was presented with multiple bruises for one month. He was incidentally noted to have raised absolute eosinophil (2.30 $x10^9$/L) with normal platelet count (433$x10^9$/L). He has no family history of bleeding disorder. Investigation showed a normal coagulation profile with prolonged bleeding time. Clot retraction appearance was poor with normal clot retraction time observed. Platelet aggregation study using whole blood impedance method showed no aggregation in response with collagen 1 ug/ml, 5 ug/ml, borderline level with ADP 5.0 uM, 10 uM, and normal response with arachidonic acid 0.5 mM and ristocetin 0.25 mg/ml, 1.0mg/ml compared with control. Correlating with history and FBC results, APDE is likely. Patient was treated with anthelmintics and subsequently, symptoms and eosinophils count (0.2$x10^9$/L) recovered. *Discussion:* APDE is characterised by eosinophilia with normal coagulation profile but increased in bleeding time. Platelet aggregation test commonly shows normal platelet aggregation with ristocetin, reduced aggregation with ADP and no aggregation seen with collagen. Due to its benign course, empirical use of anthelmintics is beneficial together with reassurance to the patient. In conclusion, high index of suspicion should be exercised in children who experienced unexplained bruising with eosinophilia.

HM31: Macrothrombocytopenia in a 21-year-old Male with DiGeorge Syndrome and Tetralogy of Fallot: A case report

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Introduction: DiGeorge Syndrome is a rare genetic disorder caused by a 22q11.2 deletion, resulting in various clinical features, including heart defects, immunodeficiency, characteristic facial features and haematological abnormalities. This case report presents a unique observation of macrothrombocytopenia in a 21-year-old male with DiGeorge Syndrome and co-existing Tetralogy of Fallot, a congenital heart condition. Despite the thrombocytopenia, the patient did not experience significant bleeding complications, even during major surgical interventions. *Case Report:* The patient, diagnosed with DiGeorge Syndrome, had a history of Tetralogy of Fallot (TOF), comprising pulmonary stenosis, ventricular septal defect, right ventricular hypertrophy, and transposition of the aorta. He had his TOF corrected at the National Heart Institute. Notably, he exhibited persistent thrombocytopenia with a 60-80 x 10^9/L platelet count and giant platelets. The patient had no bleeding issues in various surgeries, including dental and major cardiac procedures. *Discussion:* Macrothrombocytopenia is a common finding in DiGeorge Syndrome, associated with heterozygosity for the GPIb gene deletion. Patients with DiGeorge Syndrome experience less severe thrombocytopenia and milder bleeding tendencies than those with Bernard-Soulier Syndrome (BSS), who exhibit more profound thrombocytopenia and significant bleeding. In conclusion, this case report highlights the co-occurrence of macrothrombocytopenia in a 21-year-old male with DiGeorge Syndrome and Tetralogy of Fallot, with no significant bleeding complications observed despite marked thrombocytopenia. Peripheral smear evaluation is crucial to diagnose and prevent unnecessary thrombocytopenia testing quickly. Further research is needed to understand the causes of platelet abnormalities in this rare genetic disorder.

HM32: Evaluation of Carestrat ™ S1 analyser Biosensor quantitative assay of G6PD activity and establishment of reference range for point of care testing in diagnosis of G6PD deficiency

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Introduction: The requirement for a reliable and rapid qualitative assay to detect glucose-6-phosphate dehydrogenase (G6PD) deficiency at point of care is rapidly emerging, especially where the epidemiology of G6PD deficiency and P. vivax overlap. Anti-malarial for treating and preventing relapse disease caused by P. vivax, such as Primaquine and Tafenoquine, may also cause haemolysis in G6PD deficient individuals and in the carrier state. Thus, WHO recommends G6PD activity assessment before administration of these drugs to any patient. *Methods:* 195 neonates cord blood samples (155 normal and 40 G6PD deficient) analysed by OSMMR2000D G6PD assay in Haematology Unit, Department of Laboratory Diagnostic Services, UKMMC were used for evaluation of detection of G6PD deficiency. One drop of blood sample (7-10ÒL) was applied onto G6PD test strip and another onto Hb test strip and measurements were done on CareStart™S1 Analyzer simultaneously giving the final result of G6PD activity in Unit/gram Haemoglobin (U/gHb). The G6PD activities measured by this method were then compared with OSMMR2000D G6PD assay method. *Results:* The normal mean of G6PD activity by CareSTART™S1 was 8.46 U/g. The cut-off to classify G6PD deficiency were <0.9 U/gHb and <5.2 U/gHb for severe and moderate deficiency (10% and 60% of normal mean respectively). Pearson's correlation study showed strong correlation coefficients between CareSTART™S1 analyser and OSMMR2000-D (r = 0.830). The sensitivity and specificity of the CareStart™S1 analyser were 72.5% and 100%, respectively. *Conclusion:* This study showed CareStart™S1 analysers are comparable to the established method with all the advantages of a point-of-care testing.

HM33: Effect of umbilical cord-derived mesenchymal stromal cells conditioned medium on the cellular senescence of normal human dermal fibroblast

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Introduction: Cellular senescence refers to the irreversible growth arrest and progressive deterioration in cellular function. Fibroblast is commonly used in cellular senescence study. Mesenchymal stromal cells (MSC) are multipotent cells found in various human tissues which can secrete bioactive factors for tissue homeostasis. In this study, we evaluated the anti-aging properties of MSC in senescent Normal Human Dermal Fibroblast (NHDF). *Materials & Methods:* NHDF was treated with 200µM hydrogen peroxide (H_2O_2) for 2 hours and allowed recovery for 5 and 7-days to develop senescence. Characterisation of senescent NHDF was done subsequently. Senescent NHDF was further exposed to umbilical cord-derived MSC conditioned medium (UC-MSC CM) for 48 hours. A series of functional assays was done on senescent NHDF post UC-MSC CM treatment. Supernatant of senescent NHDF treated with UC-MSC CM was also collected for secretome analysis. *Results:* H_2O_2-treated NHDF exhibited hallmarks of senescent cells. After treatment with UC-MSC CM, the characteristics features of senescent NHDF were shown to be improved by decreased senescent and beta-galactosidase gene expression and increased cell proliferation. However, no significant changes were seen on the telomere length and telomerase activity of senescent NHDF after UC-MSC CM treatment. Secretome profile analysis of supernatant from senescent NHDF demonstrated increase in cytokines (eg. Stem Cell Factor, Epidermal Growth Factor Receptor) involved in cell proliferation. *Discussion:* MSC CM is able to ameliorate the senescent features in treated NHDF. Secretome analysis suggested that MSC secreted bioactive factors regulating cell proliferation to exert anti-aging effects on the senescent NHDF.

HM34: Richter's transformation of chronic lymphocytic leukaemia in bone marrow

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Introduction: Richter's transformation (RT) is defined as the development of a high-grade lymphoma in patients with a previous or concurrent diagnosis of chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) and occurs in 2-10% of patients with CLL. It is usually characterised by sudden clinical deterioration and marked multifocal lymphadenopathy (>70% of patients have enlarged lymph nodes). Here we highlight a case of RT that occurred primarily in bone marrow, with no lymphadenopathy. *Case report:* A 69-year-old man diagnosed with CLL in 2004 and was monitoring follow-up with no active treatment. He was otherwise well until he presented with constitutional symptoms and severe anaemia in 2022. There were no palpable lymph nodes and PET scan showed diffuse hypermetabolic marrow, hepatosplenomegaly and no FDG avid lymph nodes. A bone marrow biopsy showed Diffuse-Large B cell Lymphoma and he was treated accordingly. *Discussion:* RT is usually diagnosed from a lymph node biopsy, as the majority of the patients present with enlarged lymph nodes. Primary bone marrow involvement alone has rarely been reported. Due to availability of PET scan and its nifty use in diagnosis and management of lymphoma, bone marrow assessment for staging/monitoring is no longer routinely performed. FDG-PET scan has a negative predictive value of 97% in a lesion with standard uptake value (SUV) of < 5, thus a non-biopsy approach is supported for these lesions. However, a bone marrow biopsy is still indicated in patients with a negative PET-CT scan and the relevance of it is illustrated in the above case.

HM35: Comparison study of the rates of microscopic slide review in a single laboratory

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Introduction: The International Society for Laboratory Haematology (ISLH) has suggested a list of criteria prompting for action following automated complete blood count and white blood cells (WBC) differential analysis. Many laboratories have modified these guidelines to suit their local needs. The objective of this study was to evaluate whether the screening rules (SR) set-up by a laboratory have reduced the number of microscopic slide reviews (MSR) after they were revised. *Materials & Methods:* This study was performed in a private laboratory that receives samples mainly for outpatient care. Revised SR were established for WBC, mean cell haemoglobin, mean corpuscular haemoglobin concentration, platelet and automated WBC differential (data not shown). The analysers' suspected flags were excluded in this study. The rate of MSR in November 2022 was compared with the rate of MSR in May 2023 which represented the pre- and the post-period implementation of revised SR. Samples were assayed on Sysmex analysers and the MSR were performed by laboratory scientists. *Results:* The MSR rate had dropped from 3.8% (600 out of 15,748 samples) to 1.2% (331 out of 26,540 samples) without occurrence of false positive and negative findings. *Discussion:* The interest of this study is to reduce the number of MSR, especially in a laboratory that receives samples ranging from 1000 to 2000 samples per day, without sacrificing the quality of patient care. The revised SR have improved the laboratory's efficiency and were considered sufficient. This could be attributed to the origin of samples. Generally, the outpatient samples have less probability of having abnormal findings.

HM36: Waldenstrom Macroglobulinemia in a chronic anaemic patient: A case report

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Introduction: Waldenstrom Macroglobulinaemia (WM) is defined as Lymphoplasmacytic lymphoma (LPL) with bone marrow involvement and IgM monoclonal gammopathy of any concentration. *Case report:* A 57-year-old Malay man presented with long history of chronic anaemia without significant bleeding. Full blood picture shows normochromic normocytic anaemia. Serum and urine protein electrophoresis showed IgM Kappa paraproteinemia (11.8g/L in May 2022 and 13.8g/L in February 2023) and Kappa light chain paraproteinuria (0.16g/L in February 2023). Bone pain, pathological fracture, constitutional symptoms, lymphadenopathy and organomegaly were absent. Initially he was diagnosed as IgM Monoclonal Gammopathy of Undetermined Significance (MGUS) and bone marrow examination was done later in May 2023. Bone marrow aspiration was haemodiluted, but trephine biopsy reveals hypercellular marrow with infiltration by abnormal small lymphoid cells (~30%) that are positive for CD20, CD43, CD23 (heterogenous) with only kappa light chain expression and exhibit low Ki67 (<30%); and negative for CD5, CD10, Cyclin D1, and BCL6. Mast cells were also increased. These findings are consistent with lymphoplasmacytic lymphoma. Together with bone marrow involvement and IgM monoclonal gammopathy, the diagnosis of Waldenström macroglobulinemia is made. However, the patient defaulted on further follow up. *Discussion:* Adverse outcome has been associated with advanced patient age, peripheral blood cytopenias (especially anaemia), poor performance status, high β2-microglobulin levels, high (>7.0g/dL) serum paraprotein level, and others. In this case, the patient already had chronic anaemia and paraproteinemia at encounter to warrant earlier and active bone marrow assessment to workup for LPL/WM. This is prudent to provide accurate and timely management for the patient.

HM37: A contemplation to initiate anticoagulant treatment in a pseudothrombocytopenia patient

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Introduction: Pseudothrombocytopenia is an in vitro phenomenon when platelet clumps are formed by spurious activation of coagulation in vitro. This laboratory artifact can be identified based on peripheral blood film (PBF) review, using a different anticoagulant than ethylenediaminetetraacetic acid (EDTA) for blood collection or by temperature control of 37°C before testing. *Case report*: A 63 years old gentleman was initially admitted for work up on his sudden left sided body weakness post amputation of bilateral lower limbs. Patient otherwise had no bleeding history. Physical examination revealed a pulsating abdomen suggesting abdominal aortic aneurysm. No other remarkable finding noted. His abdominal ultrasound confirmed abdominal aortic aneurysm with mural thrombus. However, he was incidentally noted to have thrombocytopenia with platelet count of $35x10^9$/L in EDTA tube. PBF showed many platelet clumps that cause pseudothrombocytopenia. Platelet measurement then repeated in sodium citrate tube with platelet count of $94x10^9$/L and later in lithium heparin tube with platelet count of $133x10^9$/L. Despite PBF still showed presence of platelet clumps in these two different anticoagulants, lesser degree of platelet clumps seen in both tubes with lithium heparin tube showed the least. Patient was subsequently started on T Apixaban 5mg BD at platelet level of $100x10^9$/L. *Discussion*: Peripheral blood smear review is an important method to identify pseudothrombocytopenia when thrombocytopenia persisted in different anticoagulants. Failure to identify pseudothrombocytopenia can result in further unnecessary workup and inappropriate treatment. Effort to repeat platelet measurement in different anticoagulant may reduce the artifact and indirectly assist clinician in treatment.

HM38: Distribution of thalassaemia cases based on Hb analysis in Selangor - A three years' experience

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Introduction: Thalassaemia is a heterogenous group of genetic disorders affecting haemoglobin synthesis. It is autosomal recessive and one of the commonest genetic conditions in Southeast Asia. In Malaysia, the current estimation shows that 6.8% of Malaysians are Thalassaemia carriers. *Objective:* The aim is to categorise samples according to collection centres, to identify the type of cases sent for thalassaemia screening and to report the distribution of thalassaemia cases in Selangor. *Materials & Methods:* A retrospective data collection is done from the 1st Jan 2019 until 31st December 2021. A total of 31350 blood samples were obtained from government health clinics and hospitals in Selangor. These samples were analysed by Capillary Electrophoresis and/or High Performance Liquid Chromatography. *Results:* Most samples received were from government health clinics with the majority of them were from Form 4 screening programme. Findings were categorised into Thalassaemia trait and Thalassaemia disorder. For Thalassaemia carrier, the highest was suspected alpha thalassaemia carriers (58.8%) followed by HbE heterozygous (10.3%) and Beta thalassaemia trait (9.6%). For thalassaemia disorders, the highest was Hb H disease (0.5%) followed by Hb E beta thalassaemia (0.4%) and Hb H-Hb Constant Spring (0.2%). *Discussion and conclusion:* This study highlights the current trend of Thalassaemia in Selangor based on Selangor Thalassaemia database 2019-2021. Through this data, we can compare our data with Malaysian Thalassaemia Registry 2018 results that showed Selangor had the second highest number of cases in Malaysia. With that, we are able to estimate the burden of Thalassaemia in Selangor.

HM39: The genetic landscape relapse B-cell acute lymphoblastic leukaemia in Institute for Medical Research, Malaysia

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Introduction: Despite the high success rates of current B-cell acute lymphoblastic leaukaemia (B-ALL) treatment, a small percentage of patients experience relapse. We retrospectively analysed data in our institute to identify the significant chromosomal translocations in relapse B-ALL. *Materials & Methods:* We identified 35 paired samples of B-ALL at the time of diagnosis and relapse from 2015 until 2022. The demographic, clinical status and chromosomal translocation study data were collected. The RNAs were extracted using QIAamp RNA Blood Mini Kit. The chromosomal translocations were identified using either reverse transcriptase polymerase chain reaction (PCR) Hemavision 28N or real-time PCR Quandx Q30. *Results:* The male-to-female ratio was 1.7:1 with a median age of 5 years old. The median for total white blood cells at diagnosis was 10.8x10^9/L. Seventy-seven percent (27/35) of the cases showed no chromosomal translocation both at diagnosis and relapse. Meanwhile, seventeen percent (6/35) had *ETV6::RUNX1* and six percent (2/35) had *BCR::ABL1* at diagnosis. Among those with positive findings at diagnosis, six cases had persistent same genetic mutation at relapse which are eleven percent for *ETV6::RUNX1* and six percent for *BCR::ABL1*. The other two cases of *ETV6::RUNX1* identified at diagnosis eventually had negative findings later at relapse. *Discussion:* Chromosomal translocation in B-ALL is useful to risk-stratify patients at the time of diagnosis. However, studies on other biomarkers with prognostic and therapeutic significance are needed. Advanced tests such as high throughput deep sequencing technologies may help to stratify those patients at relapse. Hence, accurately targeted therapy can be given in the future.

HM40: A rare encounter with peculiar characteristic: Acute promyelocytic leukaemia with bcr3 isoform of *PML::RARA* - A case report

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Introduction: Acute promyelocytic leukaemia (APML) with the bcr3 isoform of *PML::RARA* is a rare and distinct subtype characterised by leukocytosis, unique morphology and prognostic significance. *Case report:* Here we report a case of a 56-year-old female, presented with lethargy, bicytopenia with no significant bleeding tendencies. She was diagnosed with right renal cell carcinoma with distant metastasis in 2019. Her FBC showed leukocytosis (42.28x10^9/L) with anaemia and thrombocytopenia. Her peripheral blood film revealed 85% blasts with some displayed bilobed and irregular nuclei. Occasional blasts exhibited cytoplasmic vacuolation. No obvious Auer rod or faggot cells seen. Bone marrow aspiration showed 90% blasts. Peroxidase stain was positive and immunophenotyping revealed a blast population with heterogeneous CD34 and HLA-DR expression which are not typical of APML. cyMPO, CD13 and CD33 were positive. Molecular study confirmed APML with presence of translocation (15;17) (q24;q21)(*PML::RARA*) with bcr3 isoform. Conventional karyotyping showed translocation (15;17) (q24;q21). FLT3-internal tandem duplication (*FLT3::ITD*) mutation was positive. All-trans retinoic acid (ATRA) was started based on suspicion of APML from blood film. However, she developed differentiation syndrome and succumbed to death eight days after ATRA. *Discussion:* Here, we present a case report of a patient diagnosed with APML with bcr3 isoform of *PML::RARA*, emphasising the challenges in the diagnosis and prognosis significance. High index of suspicion based on FBC and morphology prompt early diagnosis and treatment.

HM41: Atypical presentation of acute B-lymphoblastic leukaemia in adolescent: A case report

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Introduction: Acute B-lymphoblastic leukaemia (B-ALL) typically present with symptoms of marrow failure, cytopenia and white cell counts either decreased, normal or raised. Hypereosinophilia is one of the atypical presentations of B-ALL, which accounts for less than 1% of cases. This may cause delay in diagnosis and appropriate management if it is not recognized. *Case report:* A 15-year-old boy presented with fever and cough for a week. Clinically the patient had mild hepatomegaly. Full blood picture showed normal haemoglobin, thrombocytopenia, hyperleucocytosis (White cell count $118x10^9$/L) with hypereosinophilia (60%), neutrophilia, monocytosis, and no blast present. Bone marrow aspiration showed 66% eosinophils with abnormal morphology and 1% blasts, consistent with immunophenotyping findings. The patient was treated for Hypereosinophilic Syndrome and was given anti-helminthic and immunosuppressant. Trephine biopsy however revealed diffuse infiltration of eosinophils, together with >20% B-lymphoblasts, confirmed by immunohistochemistry. Molecular studies were negative for all 28 common translocations, *PDGFRA* gene, *BCR::ABL1, JAK2V617F* and Calreticulin (Exon9) mutations. Cytogenetic studies showed a normal male karyotype (46XY). Chemotherapy was commenced, however complicated with heart failure, leading to his death. *Discussion:* B-ALL presenting with eosinophilia is associated with aggressive disease and poor outcome. This report highlights the importance of early recognition of this atypical presentation for appropriate management to be instituted promptly. This case of B-ALL was only identified by trephine biopsy, causing further delay in diagnosis as bone marrow aspirate and immunophenotyping did not reveal excess of blasts.

HM42: A case of chronic myeloid leukaemia with a rare rearrangement variant of micro *BCR::ABL1* (e19a3) fusion transcript

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Introduction: The hallmark of Chronic Myeloid Leukaemia (CML) is the presence of the *BCR::ABL1* fusion gene originating from the t(9;22) chromosomal translocation. The encoded fusion protein may be different in size, based on the breakpoint in the *BCR* gene. 95% of the breakpoints expressed p210 protein (major) while 1-2% encodes p190 protein (minor). The other isoforms including micro p230 transcript, are exceedingly rare. *Case report:* A 35-year-old male presented with symptomatic anaemia and massive splenomegaly. His haemoglobin was low (6.7 g/dL) with hyperleukocytosis (white cells count of 97×10^9/L, predominantly 91% neutrophils) and mild thrombocytopaenia (124 x 10^3/uL). The peripheral blood and bone marrow aspirate morphology revealed classical features of CML in chronic phase. The cytogenetic analysis showed 46 XY but failed to exclude any chromosomal abnormality due to the suboptimal yield of three metaphase cells. Meanwhile, the fluorescence in situ hybridization (FISH) analysis for *BCR::ABL1* and reverse transcriptase-polymerase chain reaction (RT-qPCR) using QuanDx® screening kit were negative. Subsequently, we repeated the test using HemaVision® -28N, which showed a p230 micro *BCR::ABL1* fusion transcript (e19a3). *Discussion:* The p230 *BCR::ABL1* (e19a3) transcript is extremely uncommon. To our knowledge, this is the first case reported in Malaysia. Managing this patient is challenging due to the limited PCR primers, which leads to inaccurate diagnosis. Furthermore, the monitoring of *BCR::ABL1* transcripts with rare isoforms represents a unique clinical challenge in CML, compounded by the lack of an IS conversion due to its rarity leading to difficult disease monitoring and decision-making in the clinical settings.

HM43: The molecular diversity of the beta-thalassaemia syndrome in Malaysia: A review at a referral centre

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Introduction: Beta thalassaemia is a common monogenic disease and represents a significant health burden in Malaysia. The development of molecular techniques has made it possible to define the molecular pathology of beta-thalassaemia syndrome. Therefore, this study was conducted to characterize the molecular changes in the beta-globin gene. *Materials and Methods:* For this study, all valid referral cases from 2011 to 2015 were reviewed. Molecular analysis was performed accordingly using an Amplification Refractory Mutation System (ARMS), gap-PCR, direct DNA sequencing, and Multiplex Ligation-dependent Probe Amplification (MLPA) to characterize the genetic alterations of the beta-globin gene cluster. *Results:* A total of 2954 cases were reviewed and selected for this study. Of these 70.2% (2075/2954) cases, 68 types of beta-globin gene alterations were found, including 25 beta-thalassaemia mutations, 23 beta variants, 12 beta-globin gene cluster deletions, and eight polymorphisms. The zygosity of our cases was 46.8% (1383/2954) heterozygotes, 19.3% (571/2954) compound heterozygotes and 4.1% (121/2954) homozygotes. Highly prevalent beta-thalassaemia alleles included HbE, IVS 1-5 G>C, beta-Filipino deletion, Hb Malay, poly A (AATAAA>AATAGA), compound HbE/IVS 1-5 G>C, codon 41/42 (- TTCT), δβ-thal THAI deletion, IVS 1-1 G>T and compound HbE/Hb Malay. *Conclusion:* The application of the molecular method has provided a clearer insight into the beta-thalassaemia heterogeneity and distribution of the different molecular defects of the beta-globin gene in Malaysia. The use of appropriate individual tests can increase the effectiveness of routine mutation analysis and is useful for the management of beta-thalassaemia syndrome.

HM44: Mutational profiling of normal karyotype acute myeloid leukaemia using targeted gene sequencing

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Introduction: Chromosomal abnormalities are detected in 50–60% of patients with Acute Myeloid Leukaemia (AML) and are important predictors of prognosis and risk of relapse. However, those with normal karyotype AML (NK-AML) are deemed a unique group with distinct clinical outcomes. Identification of recurrent molecular abnormalities has improved prognostication and provided insight into NK-AML, as well as led to the discovery of novel therapeutic targets. We aim to investigate the mutational landscape of NK-AML using targeted gene sequencing. *Materials & Methods:* A cohort of 72 NK-AML patients were recruited in this study. Genomic DNA was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Germany). We use AmpliSeq™ for Illumina® Myeloid Panel target enrichment and library preparation, followed by sequencing using a NextSeq instrument. Bioinformatic analysis was performed using BaseSpace variant interpreters for SNVs and indels/duplications. *Results:* We identified at least one pathogenic variant in 66.7% (48/72) patients, and eight had multiple mutations of at least 3 pathogenic variants. The most frequently mutated gene was *NRAS* (20 patients, 27.8%) followed by *IDH1* (18 patients, 25%), *NPM1* (12 patients, 16.7%) and *DNMT3A* (10 patients, 13.8%). Eleven genes (*KRAS, JAK2, TP53, ASXL1, CSF3R, FLT3, PTPN11, CALR, CEBPA, KIT, NF1* and *PHF6*) had mutation prevalence of less than 10%. *Discussion:* Targeted gene sequencing focuses on a region of interest and restricts analyses to potentially clinically relevant genes. Therefore, it is a practical approach to identify mutational patterns that can further improve diagnostics, prognostication, treatment and disease monitoring for precision medicine in leukaemia.

HM45: A case of acquired aplastic anaemia with concurrent subclinical paroxysmal nocturnal haemoglobinuria mimicking megaloblastic anaemia at the initial presentation

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Introduction: Acquired aplastic anaemia (AAA) is a syndrome of bone marrow failure characterised by pancytopenia, marrow hypoplasia and absence of neoplasia or fibrosis. Herein we report a case of AAA with concurrent paroxysmal nocturnal haemoglobinuria (PNH) that was initially diagnosed as megaloblastic anaemia. *Case report*: The patient was a 23-year-old man with no known medical illness, presented with lethargy, reduced effort tolerance, palpitation and somnolence for two weeks. Physical examination revealed no organomegaly, no palpable lymph nodes and no physical abnormalities. Full blood picture showed pancytopenia, oval macrocytes and hypersegmented neutrophils. The serum vitamin B12 was low. A diagnosis of megaloblastic anaemia was made. He received subcutaneous cobalamin injection for one week but the response was poor despite normalization of vitamin B12. The pancytopenia persisted. ANA and anti-dsDNA were negative. Virology for hepatitis and HIV tests were negative. A bone marrow biopsy was performed. The morphologic examination of bone marrow showed profound hypocellular marrow that consists of mainly adipose cells with residual haematopoietic cells. Dysplasia, fibrosis, tumour clumps, lymphoma cells and excess of blasts were not observed. Flow cytometry of the peripheral blood showed presence of PNH clone (13.1%). Karyotyping was unsuccessful due to insufficient cells. The diagnosis was revised to AAA with concurrent PNH disease. The patient was given supportive therapy and planned for haematopoietic stem cell transplant with a matched related sibling. *Discussion*: Comprehensive evaluation is important for a correct diagnosis. AAA and PNH are intimately linked, with approximately 50% of patients with AAA harbouring a low level, subclinical PNH clone.

HM46: Atypical lack of CD4 expression blastic plasmacytoid dendritic cell neoplasm (BPDCN) in HIV patient: a diagnostic challenge

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Introduction: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive rare disorder that arises from plasmacytoid dendritic cells (PDCs) with rapid cutaneous, bone marrow involvement and leukaemic dissemination. *Case report:* We report a case of a 33-year-old gentleman with underlying HIV with severely low CD4 count and latent syphilis presented with pancytopenia. Full blood picture showed pancytopenia and the presence of a few abnormal large mononuclear cells, with abundant basophilic cytoplasm and multiple cytoplasmic vacuolations. Trephine biopsy, immunohistochemistry and bone marrow aspirate immunophenotyping findings showed 64% of cells were positive for CD38, CD123, CD43, CD56 but negative for CD4 and other markers. The morphologic and immunophenotypic suggestive of BPDCN with an atypical lack of CD4 expression and cutaneous manifestation. Cytogenetic analysis revealed complex karyotypes and 8q24/*MYC* gene rearrangements. The patient succumbed due to disease severity. *Discussion:* This case was scarce and had limited literature reviews. When it was detected, extensive exclusion of the significant expression of myeloid and lymphoid-specific markers was required before reaching the final diagnosis. Immunophenotypic diagnostic criteria for BPDCN required the expression of CD123 and one of the other PDC markers in addition to CD4 and/or CD56. The lack of CD4 BPDCN is extremely rare (approximately 8%). 8q24/*MYC* rearrangements were reported in 10 to 15% of BPDCN and may play a role in BPDCN pathogenesis with undetermined prognostic significance.

HM47: Next generation sequencing analysis of chronic myeloid leukaemia patients who failed second generation tyrosine kinase inhibitor

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Introduction: The causal molecular evolution for a subset of individuals with Chronic Myeloid Leukaemia (CML) to lose molecular remission is still unknown. In this study, our goal was to explore the molecular mechanisms involved in resistance to tyrosine kinase inhibitor (TKI) in patients who failed second generation therapy. *Materials & Methods:* Eight CML patients who failed second generation TKI were identified and labeled as non-responders. After the samples were processed and checked for purity, the RNA samples were sequenced on the Ilumina Novoseq 6000 system (Ilumina, California, USA) with an average of approximately 133 million passed paired reads at 100bp in length, per sample. The paired-end reads were aligned to the human reference genome (version hg38/GRch38) using the Ilumina DRAGEN (Dynamic Read Analysis for GENomics) Bio-IT platform and used for variant analysis. Genes that demonstrated a Log_2 fold-change of ≥3 and p≤0.01 were identified as differentially expressed genes (DEGs). *Results:* There were a total of 201 DEGs discovered with 87 genes upregulated and 114 genes downregulated. *BCR::ABL1* was detected in all the non-responders. *TPM4::KLF2* and *CCDC32::CBX3* were the next most common fusion genes identified (5 of 8). A total of 21,782 (3.5%) variations were determined to be present only in the non-responder group. The DEGs were enriched in several pathways which included histone acetylation/deacetylation (HDACs/HATs), cellular senescence and RNA polymerase regulation. *Conclusion:* This preliminary analysis showed that individuals who failed second generation TKI express a unique genetic profile. Analysis using a larger sample size is necessary for further validation.

HM48: Gaucher's disease, a revised diagnosis from bone marrow specimen

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Introduction: Gaucher's disease (GD) is an autosomal recessive disorder, characterised by β-glucocerebrosidase (GBA) enzyme deficiency due to *GBA* gene mutation leading to glucosylceramide accumulation in lysosomes of reticuloendothelial cells. It is common in Ashkenazi Jews, but rare in Malaysia with estimated 0.31 cases per 100,000 live births. Clinical presentation includes hepatosplenomegaly, cytopenia, bone diseases, neurological symptoms and other systemic manifestations. *Case report:* A 3-year-old Malay girl with a history of closed left humerus fracture after a trivial fall 6 months prior, was brought to medical attention for progressive abdominal swelling. Physical examination showed massive hepatosplenomegaly. Full blood count reported as moderate anaemia with mild thrombocytopenia. Lytic lesions with poor callus formation were seen from serial X-ray of the fracture site. She underwent bone marrow (BM) examination for possible Langerhans Cell Histiocytosis (LCH). While waiting for the report, she was treated clinically for multisystem LCH with oral Prednisolone and intravascular Vinblastine. BM findings later revealed a diffuse infiltration by CD163 positive histiocytes which are negative for S100 and CD1a stains. The diagnosis was revised as GD which was confirmed by a very low activity of GBA enzyme and homozygous pathogenic missense mutation of the *GBA* gene at c.1072C>G (p.Pro358Ala). She was referred to the Genetic Clinic for further management. *Discussion:* GD is a lysosomal storage disorder with enzyme replacement therapy as the primary treatment. It could be misdiagnosed as other diseases due to its overlapping presentation. Careful examination of the BM specimen will be helpful for the clinician thus improving the outcome of the patient.

HM49: Pancytopenia in a poorly chelated transfusion-dependant thalassaemia patient

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Introduction: The severity of thalassaemia intermedia depends on the degree of imbalance between α-globin chains as well as other genetic and environmental factors that modify the natural history of the disease. Iron overload-associated organ damage in transfusion-dependent thalassaemia is a well-known phenomenon, particular in poorly chelated patients. Here we report a case of bone marrow failure secondary to extensive bone marrow iron deposition. *Case report:* This is a case of a 26-year-old Malay female with transfusion-dependant Hb E/□ thalassaemia. She presented with left thigh pain and swelling and history of intermittent bleeding of the gums with maxillary pain. A diagnosis of left thigh periosteal haematoma was made. Recent blood workup showed persistent pancytopenia. Bone marrow examination revealed extensive clusters of haemosiderin laden macrophages in place of normal haematopoietic elements. Additionally, she had other complications of iron overload including hypogonadotrophic hypogonadism with primary amenorrhea and hypoadrenalism. Most recent T2 MRI also revealed severe iron overload of the heart and liver. *Discussion:* Although not common, bone marrow failure secondary to iron overload in transfusion dependent thalassaemia patients have been reported. The pathogenesis of bone marrow failure in iron overload is said to be primarily due to increased ROS production causing damage to bone marrow stem cells. This case further exemplifies the need for adequate chelation and management of reversible iron overload toxicities. Besides serum ferritin, organ-specific diagnostic modalities must be used together to assess the severity of iron overload in specific organs to prevent long-term complications in patients with regular blood transfusions.

HM50: The neutrophil-lymphocyte ratio as a biomarker for disease severity in COVID-19 patients

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Introduction: Selected full blood count (FBC) parameters may reflect an underlying hyperinflammatory response driving a severe hypercytokinaemia in severe COVID-19 infection. We aim to determine the usefulness of leukocyte counts and their differential which is simple and readily available parameters in all ranges of automated haematology analysers with disease severity and outcomes amongst COVID-19. *Materials and Methods:* This was a retrospective study involving molecularly confirmed COVID-19 patients admitted to Hospital Kuala Lumpur (HKL) from 1st June 2021 until 31st December 2021. Data patients who fulfilled the inclusion criteria and had done all investigations intended in this study were included. Their demographic data and laboratory parameters were retrieved and analysed. *Results*: There were 283 patients' data included. Their mean age was 54.10 ±14.9. Males and females were equally affected with the majority being Malays, 49.1% (n=139). About 61.1% of patients (n= 173) were in category 4 at their presentation. Statistical analysis showed there was a significant difference between TWCC and COVID-19 categories (p-value 0.002). The median TWCC was statistically significantly lower in category 3 (mild) as compared to category 4 (moderate) and category 5 (severe) as evidenced by the post hoc test (Bonferroni correction) with an adjusted p-value of 0.006 and 0.007, respectively. There was a significant difference between the neutrophil-lymphocytes ratio (NLR) and COVID-19 categories (p-value 0.002). *Discussion*: This study demonstrated there was a significant association between NLR with various COVID-19 categories. NLR is a cheap and robust available predictor of COVID-19 disease and can be a simple biomarker which could help the clinician to predict the COVID-19 severity. With early and correct patient triage the clinician can be able to give optimum management for a better outcome.

HM51: Differentiation of hiPSCs and hESCs derived haematopoietic stem and progenitor cells into macrophages and its functional comparison

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Introduction: Macrophages are potential candidate for cell-based therapy. Induced pluripotent stem cells (iPSCs) can be the alternative cell source in deriving macrophages to overcome the ethical controversy of human embryonic stem cells (hESCs). In this study, we aim to validate if the hiPSCs derivatives resemble the hESCs derivatives. *Methodology:* We differentiated the hiPSCs/hESCs derived haematopoietic stem progenitor cells (HSPCs) into macrophage-like cells using StemAPEL2 medium supplemented with SCF, IL-3, IL-6 and M-CSF for 10 days; followed by M1/M2 macrophage polarisation assay using IFN-γ and LPS, or with IL-4 respectively. The morphology, immunophenotype profile and phagocytic activity of the differentiated cells were evaluated. *Results:* The hiPSCs-HSPCs produced significantly higher M0 macrophage than hESCs-HSPCs ($p = 0.02$) and both showed comparable morphological, immunophenotype features (25F9 and CD45) and phagocytosis activity. The hiPSCs derived M1 and M2 subsets expressed significantly higher M1 marker - CD86 (53.9 ± 4.5% and 17.7 ± 1.1%, $p = 0.001$), and co-expression of M2 markers - CD163 and CD206 (45.0 ± 5.1% and 1.84 ± 0.3%, $p = 0.001$) than the hESCs derivatives. The bias of hiPSCs derived macrophages towards M2 subtypes is likely to be caused by the use of MCSF in the culture which favour the differentiation towards anti-inflammatory M2 subtype. *Conclusion:* Macrophages derived from hESC and hiPSC showed comparable morphological, immunophenotype features and phagocytosis activity. Interestingly, hiPSCs showed higher expression of M2-macrophages which their clinical applications are widely investigated in various clinical trials. Deriving macrophages from hiPSCs with serum-free protocol could provide un-exhaustible source for therapeutic applications.

HM52: The Crimson Conundrum: A case report of acquired haemophilia A from a tertiary centre in Malaysia

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Introduction: Acquired Haemophilia A (AHA) is a bleeding illness caused by inhibitors that neutralize coagulation factor VIII (FVIII) with potentially to be life threatening. Incidence of AHA is extremely rare, with only 1.5 cases reported per million people annually. *Case report:* We report a case of 84-year-old lady with underlying diabetes mellitus, hypertension, and chronic kidney disease. She initially presented with melena and altered mental status. Her haemoglobin level was 4.3 g/dL, platelet count was 240 x 10^9/L and WBC was 22.6 x 10^9/L. Endoscopy showed forest 2A/3 ulcers while CT brain showed no intracranial haemorrhage. She was discharged well and later readmitted for hospital acquired pneumonia. During her prolonged admission she developed spontaneous bruising, large haematoma over chest and abdomen, and blood oozing from the cannulation site. Coagulation screens performed were re-reviewed and noted consistent isolated prolonged Activated Partial Thromboplastin Time (APTT) while her baseline in 2014 was normal. APTT mixing showed no correction at immediate mixing and 2 hours incubation. Factor assays showed Factor VIII level of 0% with Factor VIII inhibitor of 250 Bethesda Unit (BU). Patient succumbed to death a few days later. *Discussion:* Isolated prolonged APTT might be the initial presentation of AHA which can be missed initially. AHA is frequently confused with other life-threatening conditions thus can lead to severe morbidity or even mortality before it is correctly diagnosed. It is primarily seen in patients aged 60-80 years old. This case demonstrates the importance of having a high index of suspicion for acquired haemophilia A in elderly with persistent isolated prolonged APTT.

HM53: Verification of correction factor of platelet count in citrated tube in case of true thrombocytopenia

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Introduction: Full blood count is a fundamental test that is routinely done in healthcare settings. The recommended anticoagulant to be used is Ethylenediaminetetraacetic acid (EDTA) tube. However, EDTA has its own limitations whereby it may induce platelet aggregation and lead to pseudothrombocytopenia. Alternatively citrate tube is used to correct the pseudothrombocytopenia caused by EDTA. However, we noticed that in our setting there are many requests for repeat platelet analysis using a citrate tube in cases of true thrombocytopenia. In view of blood to anticoagulant in the citrate tube is 9:1, correction factor of 1.1 should be used to correct platelet count in the citrate tube before reporting the final result into the laboratory information system. *Materials & Methods:* This retrospective study analysed 6 months laboratory data in Hospital Melaka which encompassed true thrombocytopenia cases that have been confirmed morphologically. The main objective was to verify platelet count in EDTA and corrected platelet count in citrate tube (platelet count in citrated x 1.1) is well correlated. *Results:* The results revealed a significant positive correlation between platelet count in EDTA and corrected platelet count in citrate tube, indicating that the correction factor of 1.1 should be used when reporting of platelet in citrated tube. Furthermore, the strength of this correlation was found to be strong (r=0.926). *Discussion:* The positive correlation between platelet count in EDTA and corrected platelet count in citrate tube aligns with previous studies, suggesting that correction factor of 1.1 is to be used to correct platelet count in citrate tube. Further study comprising normal and high platelet counts are necessary to determine this correlation conclusively.

HM54: Hb Q-Thailand, α1 Codon 74 (GAC>CAC) and the Interaction; Haematological and Molecular Characterization based on Malaysian Data

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Introduction: To date, very limited published data exists on the molecular aspect of HbQ-Thailand and the interaction in the Malaysian population. Most of the data available in the literature came from Thailand and the Chinese population. HbQ-Thailand is an alpha chain variant commonly affects the *HBA1* gene with the occurrence of a leftward single α-globin gene deletion ($-\alpha^{4.2}$) in *cis*. *Objective:* This study aims to describe the haematological parameters, phenotype, and genotype characterisation of HbQ-Thailand and their interaction. *Methods:* Analysis involved fifty-three confirmed cases of HbQ-Thailand retrieved from our databases. Cases referred to the Institute for Medical Research (IMR) from 2017 to 2023. The cases were subjected to Gap-PCR and direct sequencing of the *HBA* gene for variant detection. *Results:* Majority of our cases were Chinese (n=47, 88.6%) and cases referred from Perak and Sarawak. Seven genotypes were identified; heterozygous HbQ-Thailand (n=39, 73.6%), compound heterozygous Hb Q-Thailand with alpha plus thalassaemia (n=6, 11.3%), (Hb CS, Hb Adana, Hb Westmead, and -α4.2), HbH Q-Thailand (n=5, 9.4%) and heterozygous Q-Thailand co-inheritance with beta thalasaemia (n=3, 5.7%). The mean levels of HbQ-Thailand were 28.1%, 33.0-47.30%, 82.0% and 15.75% respectively, based on CE results. We reported a rare interaction between HbQ-Thailand/ Hb Adana that presented with moderate thalassaemia intermediate phenotype. *Discussion:* The interaction of HbQ-Thailand with other molecular determinants leads to complex thalassaemia syndromes with various phenotypic features. Thus, molecular characterization is required for precise diagnosis especially for appropriate management and genetic counselling of the patients.

HM55: Exploring the clinical and morphological features of Diffuse Large B-cell Lymphoma initially diagnosed through bone marrow aspirate/ trephine biopsy: A case series

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Introduction: Diffuse large B cell lymphoma (DLBCL) is one of the most common mature B cell lymphoid neoplasms. Here we present three cases of DLBCL initially diagnosed through bone marrow aspiration (BMA) and trephine biopsy. *Case report:* Case 1: A 59-year-old lady presented with dysphagia. Clinically she has unilateral tonsillar mass. No lymphadenopathy or hepatosplenomegaly. Full Blood Picture (FBP) showed severe anaemia and thrombocytopenia with marked RBC agglutination. Direct Coomb's test positive (3+) with high LDH level. A few suspicious mononuclear cells seen in marrow aspiration. Immunophenotyping revealed 0.7% suspicious B-lymphoid population. Trephine biopsy showed a few individual large CD20+ cells. Later tissue biopsy of the tonsillar mass revealed DLBCL, germinal centre subtype. Case 2**:** A 62-year-old lady presented with prolonged fever and weight loss. She has no lymphadenopathy or hepatosplenomegaly. FBP showed pancytopenia. BMA revealed a few suspicious abnormal mononuclear cells. Immunophenotyping was not done. Trephine biopsy showed large cells expressing CD20, BCL6, MUM1, CMYC and BCL2. Findings are in favour of DLBCL non germinal centre B-cell (non-GCB) phenotype with dual expression of CMYC and BCL2. Case 3: A 74-year-old man presented with on and off fever, lethargy, loss of appetite and loss of weight, no organomegaly. FBP showed leucoerythroblastic, anaemia and thrombocytopenia. Bone marrow aspiration was suboptimal for interpretation. Immunophenotyping was not done. Trephine biopsy showed large abnormal lymphoid cells expressing CD20, BCL 2 with high Ki67 but negative for CD10, and C-MYC. Trephine biopsy findings best fit DLBCL, activated B cell (non-GCB) type. *Discussion/Conclusion:* DLBCL has various clinical manifestation. In cases where there is no organomegaly or accessible tissue mass and obtaining a tissue biopsy isn't feasible, the importance of BMA and trephine biopsy becomes paramount for lymphoma diagnosis. Thorough examination of BMA, trephine biopsy and immunophenotyping, improves DLBCL detection, leading to early diagnosis and accurate staging even in the absence of evident organ enlargement or masses.

HM56: Non deletional Hb H disease (co-inheritance Hb Constant Spring and uncharacterised alpha gene deletion): Molecular diagnostic challenges in hospital setting

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Introduction: Haemoglobin H (HbH) disease is an α-thalassaemia intermedia resulting from a variety of genetic abnormalities and clinical phenotypes. We report a case of thalassaemia intermedia and its molecular diagnostic challenges to arrive at a patient's diagnosis. *Case report*: A 41-year-old Malay gentleman was informed to have thalassaemia after presenting with anaemia at 7 years old. He has a strong family history of thalassaemia. He had a surgical splenectomy related to a motor vehicle accident at 23 years old and he also had a history of receiving blood transfusion on and off. Recently he was admitted to the government hospital with a one-day history of fever, cough and diarrhoea. Physical examination revealed afebrile, no cyanosis, neither respiratory distress nor abnormal cardiac sign. However, pulse oximetry showed persistently low oxygen saturation level despite on supplemental oxygen. Patient was referred to our hospital for further investigations and management. The analysis of full blood picture, supravital stain, haemoglobin quantification and pattern by capillary electrophoresis and high-performance liquid chromatography suggested that the presumed diagnosis of HbH-Constant Spring (CS). Molecular analysis by multiplex amplification refractory mutation system polymerase chain reaction (PCR) revealed Hb CS mutation. There was no common alpha gene deletion mutation identified by Gap-PCR. Subsequently, targeted sequencing by next generation sequencing revealed co-inheritance Hb CS and uncharacterized alpha gene deletion. *Discussion*: This patient's genotype confirmation requires extensive molecular investigations at the referral laboratory. Hence, the treating physician must be well informed by the laboratory regarding the patient's presumed diagnosis, molecular screening results and expected delay to arrive at a definitive diagnosis.

HM57: A compound heterozygous Hb-G Coushatta with rare beta thalassaemia exhibiting moderate phenotype: A case report

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Introduction: Haemoglobin (Hb) G Coushatta (NG_000007.3:g.70662A>C) was reported in various populations but uncommon in Malaysia. Previous studies reported the variant as silent phenotype in either heterozygous, homozygous or co-inherited with β^+ thalassaemia. Nonetheless, we came across an unexpected laboratory finding in a Nepalese who was admitted for acute hepatitis. *Case report*: A 34-year-old Nepalese man presented with fever, abdominal pain and GI losses with the diagnosis of acute hepatitis. His full blood count (FBC) showed Hb 8.2g/dL with RBC, MCV, MCH, RDW and retics were 5.02 x 10^{12}/L, 50 fl, 16.3 pg, 20% and 2.17% respectively. Physical examination showed patient had slight pallor with massive hepatosplenomegaly. Capillary electrophoresis showed an abnormal peak in Hb D zone (92.0%) with increased HbA2 value (7.5%). No abnormal peak in high performance liquid chromatography except increased HbA2 value (88.7%) and normal HbF (1.3%). Molecular analysis of *HBB* gene sequencing revealed compound heterozygous of Codon 16 [GGC>GG-] and Codon 22 [GAA>GCA] Hb G-Coushatta mutations. Molecular analysis for common deletional and non-deletional alpha thalassaemia showed negative findings. *Conclusion:* Hb G Coushatta was reported as benign/likely benign (B/LB) variant based on ITHANET database. Compared to Codon 16, a single nucleotide deletion created frameshift with a premature translational stop codon causing loss-of-function of beta globin gene. The question on whether Codon 16 is the primary modifier in modulating moderate phenotype with superimposed infection in this patient or Hb G Coushatta could be significant likely pathogenic/pathogenic (LP/P) variant should be further explored. Further evaluation and data analysis should be considered to re-visit the variant classification based on ACMG/AMP guidelines.

HM58: Thrombotic Thrombocytopenic Purpura in Pregnancy: A case report

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Introduction: Thrombotic thrombocytopenic purpura (TTP) is a severe and life-threatening disease characterised by microangiopathic haemolytic anaemia (MAHA), severe thrombocytopenia, and symptoms related to microvascular thrombosis. *Case report*: A 34-year-old lady, gravida 8 para 3+4, presented to the emergency department at 12 weeks gestation with sudden onset of altered sensorium and fever. On examination, she was febrile, pale with a tinge of jaundice. Her blood pressure was 118/60 mmHg and heart rate of 106 bpm. Laboratory investigations showed anaemia, thrombocytopenia, and numerous schistocytes on a peripheral blood smear. Based on clinical symptoms and laboratory findings, diagnosis of TTP was made. ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) activity as part of the workup for an episode of TTP was sent to the referral laboratory, and the result obtained was low. She was immediately started on plasma exchange with fresh frozen plasma; however, her platelet count and haemoglobin did not improve. A Rituximab at a dose of 500mg was initiated. After three days of Rituximab administration, her consciousness

improved and her platelet count returned to normal on day 11. *Discussion:* TTP in pregnancy may be clinically challenging due to overlapping features with other thrombotic microangiopathies (TMAs). Ensuring correct diagnosis and management is critical because of the impact on fetal and maternal outcomes.

HM59: Identification of 619 bp deletions of beta-globin gene in two siblings with transfusion-dependent thalassaemia in Malaysia: A case report

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Introduction: Thalassaemia is an inherited haemoglobin and genetic variation underlying the disease varied in different ethnic populations and geographic locations. The 619 bp deletion (NG_000007.3:g.71609_72227del619) was first described in 1979 and is prevalent among Asian Indians and Middle Eastern descent. The variant is a rare beta zero deletion among Malaysian population and never been reported in the literature. Hence, this study reports the identification of 619 bp deletion in two siblings with transfusion-dependent thalassaemia. *Case presentation:* Two male siblings with backgrounds mixed of Malay and Pakistani aged 13 (EB113) and four (EB114) years old presented with a presumptive diagnosis of monthly transfusion-dependent HbE/beta-thalassaemia, early age at diagnosis (<2 years old), haemoglobin level <9 g/dL microcytic hypochromic RBC indices. The impression from haemoglobin analysis was of HbE/beta-thalassaemia and thalassaemia intermedia for EB113 and EB114 respectively. Molecular analysis revealed the presence of compound heterozygous states of codon 26 (**G**AG>**A**AG) HbE and 619 bp deletion, and compound heterozygous states of 619 bp deletion and Siriraj ~118 kilobase deletion with concomitant $\alpha\alpha\alpha^{anti3.7}$ mutation in EB113 and EB114 respectively. *Discussion:* With the proper diagnosis including molecular analysis, the clinical course of each thalassaemia mutation can be better recognized and correlate with the disease severity. This case report unveils the importance of molecular analysis and extant literature on 619 bp deletion in the Malaysian population.

HM60: Mixed-phenotype acute leukaemia, T/Myeloid with *TP53* deletion: A case report

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Introduction: Mixed phenotype acute leukaemia (MPAL) is rare and it posing a diagnostic and therapeutic challenges. It accounts for <3% of acute leukaemia. Herein, the case of a patient with Mixed-phenotype Acute Leukaemia, T/Myeloid with complex cytogenetic abnormalities. *Case report*: A 16-year-old male, presented with increasing bilateral neck and axillary swelling associated with constitutional symptoms. Clinically has hepatosplenomegaly with multiple lymph nodes palpable. Mediastinal mass captured by imaging study with suspicion of lymphoma. FBC showed mild leucocytosis (13.23 x 10^3/uL) with normal haemoglobin and platelet count. Peripheral blood film showed occasional suspicious mononuclear cells. Bone marrow aspiration revealed 60% of blasts with immunophenotyping showed a CD34 blasts population exhibited co-expression of T-lymphoid and myeloid lineages markers of cyCD3 and MPO. Cytogenetic studies revealed the presence of complex karyotypes and deletion 17p. Diagnosis of Mixed-phenotype Acute Leukaemia, T/Myeloid, NOS was rendered, and combine therapeutic regime was commenced. However, at day 17 post induction, he met an unfortunate end. *Discussion*: MPAL is a complex entity, characterized by co-expression of antigenic marker from different lineages. Given the rarity of this neoplasm with limited data available on association of the genomic and molecular landscape, effective therapy is challenging with prognosis remain uncertain. Historically, MPAL has inferior survival and this case report proven the disease carry dismal prognosis along with poor cytogenetic features.

6. Medical Microbiology

MM1: A case report of varicella-zoster virus meningitis with herpes zoster ophthalmicus in an adult

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Introduction: Meningitis is mostly caused by viruses, with the commonest being enteroviruses, followed by herpes simplex and varicella-zoster virus. The identification of the causative pathogen in cerebrospinal fluid (CSF) is challenging. Hence, the majority of patients received empiric antimicrobial therapy and some were discharged without a definitive pathogen diagnosis. *Case report*: A 56-year-old female with no known medical illness presented with the first episode of fitting, which was generalized tonic-clonic in nature. Prior to that, she was unwell for 3 days, complaining of left eye pain and vesicular rashes on her left forehead associated with headache and vomiting. Lumbar puncture was done. CSF was clear with normal cell count (1/mm^3), normal protein and glucose. CSF culture yielded no growth. Multiplex polymerase chain reaction (PCR) meningitis/encephalitis panel detected a varicella-zoster virus on the same day. Magnetic resonance imaging of the brain reported diffuse infective changes involving both cerebral hemispheres, likely meningitis with early hydrocephalus noted. The patient was diagnosed with varicella-zoster virus meningitis with left eye herpes zoster ophthalmicus. She was treated with intravenous acyclovir three times daily for 3 weeks, topical chloramphenicol and topical dexamethasone. Subsequently, she improved clinically and was discharged home after completion of acyclovir with follow-up appointments. *Discussion*:

Rapid multiplex PCR testing for central nervous system infection can expedite pathogen diagnosis and enhance patient care with prompt initiation of targeted antiviral therapy to prevent the development of neurological complications.

MM2: A *'Cat-Scratch'* that escape many testings: A case report of cat-scratch disease in immunocompromised patient

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Introduction: Bartonella henselae is a fastidious, intracellular Gram-negative bacilli responsible as the aetiologic agent of cat-scratch disease (CSD). *B. henselae* is a slow-growing bacterium which makes conventional culture approaches very challenging. *Case report:* Herewith we report a 30-year-old HIV-infected male presented with a typical skin lesion of angiomatosus and pyrexia. Further ultrasonic investigation revealed multiple splenic abscess but other microbiological investigation via conventional blood culture method and Bartonella serologic testing yield negative results for both IgM and IgG. Histopathology examination (HPE) test of the skin lesion was suggestive of bacillary angiomatosis that is highly suspicious of CSD. Patient was started on empirical CSD treatment for systemic infection based on clinical judgement. Subsequently, polymerase chain reaction (PCR) testing of the blood specimen at Institute for Medical Research detected the deoxyribonucleic acid of *Bartonella henselae*. *Discussion:* Diagnosis of CSD infection relies on both clinical suspicion & maximum laboratory effort to identify the aetiological agent. There are several limitations of conventional culture method and serological approach in diagnosis in CSD. Therefore, highly sensitive and specific *Bartonella henselae* PCR is now increasingly utilized for laboratory diagnosis of CSD. A constellation of symptoms might potentially appear in immune-weakened hosts including bacillary angiomatosis (BA), hepatic peliosis, splenitis and systemic illness. Thus, relevant laboratory tests should be carefully ordered to prioritise the most highly suspicious diagnosis.

MM3: Case series of bacteraemia caused by non-hydrogen sulfide producing Salmonella **species in both immunocompetent and immunocompromised patients**

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Introduction: Production of hydrogen sulfide (H_2S) is a unique character of *Salmonella.* However, several non-H2S-producing *Salmonella* species have been reported mainly from poultry meat in several countries but rarely reported from human clinical samples. We report a case series of bacteraemia due to non-hydrogen sulfide producing *Salmonella* spp. *Case report 1:* A 71-years-old man with urothelial carcinoma presented with fever, diarrhoea, and abdominal pain after recent chemotherapy. Blood culture grew a gram-negative, non-lactose fermenter organism which reacted as alkaline, acid, gas-negative and H_2S-negative on triple sugar (TSI) agar. The isolate was identified as *Salmonella* spp. by MALDI-TOF and VITEK GN and confirmed as *Salmonella* Enteritidis by 16s rRNA sequencing and serotyping by national reference laboratory. He was treated with intravenous ceftriaxone. *Case report 2:* A 37-years-old man with no-comorbid presented with prolonged fever of 2 weeks. He was treated empirically with intravenous ceftriaxone and azithromycin and had several investigations for pyrexia of unknown origin. Aerobic blood culture grew gram-negative bacilli, non-lactose fermenter organism and reactions on TSI agar were alkaline, acid, gas-negative and H2S-negative. VITEK GN and MALDI-TOF identify the organism as *Salmonella* spp. 16s rRNA sequencing and serotyping confirmed as *Salmonella enterica* serotype Paratyphi A. *Discussion:* To date, there are only a few countries that have published case reports on non-hydrogen sulfide producing *Salmonella* spp. from clinical samples. Non-H_2S-producing *Salmonella* can be misdiagnosed as *Salmonella* Typhi or even other Enterobacteriaceae. Therefore, caution is needed with the diagnosis of *Salmonella* infection. The importance of this isolate as a human pathogen requires further study and we should strengthen the surveillance of this atypical *Salmonella* spp.

MM4: A rare case of Actinomycosis with pericardial and pleural effusion caused by *Schaalia cardiffensis*

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Introduction: Schaalia cardiffensis normally colonises the mouth, digestive and urogenital tracts. It is a fastidious anaerobic, gram-positive filamentous bacilli organism that causes actinomycosis. We report a rare manifestation of actinomycosis with cardio-pulmonary involvement. *Case report:* A 44-years-old man, active smoker presented with fever, cough, and shortness of breath for 3 days. On examination, he was febrile and tachypnoeic. He had poor dental hygiene. Lung examination revealed reduced air entry bilaterally. The total white blood cells and C-reactive protein were raised. Chest X-ray showed bilateral pleural effusion and echography revealed pericardial effusion. Purulent pericardial fluid was obtained from pericardiocentesis. Pus culture grew gram-positive bacilli filamentous beaded organisms and appeared as grey, non-lysis colonies on blood agar only after 5 days of incubation under strict anaerobic condition. MALDI-TOF and VITEK ANC were unable to achieve any conclusive results. The isolate was sent to the national reference laboratory and the identification was confirmed as *Schaalia cardiffensis* by 16S rRNA gene sequencing. It was susceptible to penicillin G and ceftriaxone. He was treated with intravenous ceftriaxone for 25 days and discharged well with long term oral ampicillin-sulbactam without surgical intervention. *Discussion:* Pericardial and pleural effusion is a rare clinical presentation of thoracic actinomycosis that may evolve into cardiac tamponade or pericarditis if unrecognized and untreated. Diagnosis of actinomycosis is generally hampered by the difficulty in isolation and culture of the organism because of the strict anaerobic character of *Actinomyces spp*. Fortunately, in this case, the organism was successfully isolated from anaerobic culture and identified by molecular testing.

MM5: The association between platelet count and cytokine levels in dengue patients

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Introduction: Platelets play an important role in the immune response including the regulation of cytokines release during infection. The reduction of platelet count (thrombocytopenia) is one of the characteristics often observed in dengue patients. In this study, we aimed to investigate the relationship between platelet count and cytokine levels among dengue patients. *Materials & Methods:* This study involved 108 dengue patients admitted to Hospital Kuala Lumpur from September 2018 to October 2020. Fifty-five patients were diagnosed with severe dengue and 53 were non-severe dengue. Their clinical data was recorded and blood samples were obtained during the hospital admission for complete blood count and cytokines study. Levels of cytokines: interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor-alpha (TNF-α) were determined by using cartridge-based automated immunoassay systems. *Results:* The age of patients ranged from 18 - 67 years, with median age of 27 years. Majority of the patients were male (60.2%). Of all patients, 43.5% developed leucopenia while 35.2% had platelet count of 100 $x10^3/\mu L$ or below. Among the cytokines tested, the level of IL-10 was found significantly higher in patients with reduced platelet count (≤100 $x10^3/\mu L$) compared to patients with platelet count more than 100 $x10^3/\mu L$ (p=0.002). However, the levels of cytokines and platelet count were not associated with disease severity in this study. *Discussion:* Our results suggest that the increased levels of IL-10 is strongly associated with reduced platelet count during dengue infection and possibly contribute to the disease progression of dengue patients.

MM6: Autoimmune hepatitis screening - A scenario in Malaysia

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Introduction: Autoimmune hepatitis (AIH) is characterised by progressive inflammation and necrosis of hepatocytes that leads to a variety of phenotypes, including acute liver dysfunction, chronic progressive liver disease, and fulminant hepatic failure. Globally, the prevalence of AIH is 17.44 per 100,000.00 (12.77 for female and 2.91 for male) and the prevalence rate in Asian (12.99/100,000.00) is lower than that in European (19.44/100,000.00). Specific liver autoantibodies such as anti-soluble liver antigen/liver-pancreas antigen (anti-SLA/LP), liver-kidney-microsomal-1 (LKM-1) antibodies and liver cytosol type 1 (anti-LC1) are important biomarkers in assisting diagnosis of autoimmune hepatitis. Antibodies to soluble liver antigen (anti-SLA) are present in patients with type 1 AIH and have high specificity (99%) for the diagnosis. Antibodies to liver cytosol type 1 (anti-LC-1) occur mainly in children with severe liver disease and Anti-LKM-1 antibodies are commonly detected in the absence of antinuclear antibodies (ANA) and Smooth Muscle Antibodies (SMA) and its titre reflect disease severity and treatment response. *Objective*: To determine the seropositivity of suspected AIH patients**.** *Materials and Methods***:** This retrospective study involved 416 patients suspected with autoimmune liver diseases. Sera were tested for anti-SLA/LP antibodies, anti-LKM-1 antibodies and anti-LC1 determined by EUROLINE- Autoimmune Liver Disease (IgG) immunoblot strips – (EUROIMUN). The test kit contains test strip coated with lines of purified antigens. *Results***:** Thirty-seven (8.89%) patients were seropositive for at least one of autoimmune hepatitis autoantibodies against anti-SLA/P, anti-LC-1 and / or anti-LKM-1. Twenty- three patients were female and 14 patients were male (2: 1 ratio). Patient age ranged from 13 to 79 years old, with a median age of 49.83 years. Out of seropositive patients, 26 (70.27%) were positive to anti- LC-1 antibody, 7 (18.91%) against anti-SLA/P antibody and 4 (10.81%) against anti- LKM-1 antibody. *Conclusion*: Our findings revealed that autoimmune hepatitis was predominantly common in females and the frequency of seropositivity was relatively low in Malaysia.

MM7: A clinical audit on blood culture volume in adult patients at Hospital Melaka

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Introduction: Optimal blood culture volume (8-10ml) is recommended for the best detection of bacteraemia and fungaemia. Hence, a clinical audit was carried out at Hospital Melaka to determine the percentage of blood culture bottles with optimal volume and a target of at least 80% was set. *Materials & Methods:* Aerobic and anaerobic blood culture bottle fill volumes were measured manually using a calibrated weighing machine. The percentage of blood bottles with optimal volume was obtained. *Results:* A total of 1059 blood cultures were evaluated over 15 days and only 4% of the bottles achieved optimal volume with the mean blood volume of 3.55ml. A series of quality improvement activities was implemented over 2 months after the first audit. Strategies of change included continuous medical education to clinicians, manual bottle markings to guide the blood collectors, delivery of information to clinicians and targeted communication. Second audit was carried out 2 months after the initial audit. A total of 535 bottles were collected and 74% of the bottles achieved optimal volume with mean volume of 7.77ml. The increment of the percentage of bottles with optimal volume is significant ($p < .0005$) and there was also significant improvement in terms of mean volume ($p < .0002$) although the target was not achieved. *Discussion:* The issue of underfilled blood culture is ubiquitous in Hospital Melaka. Continuous educational and operational strategies are needed to tackle this problem. Regular monitoring and re-audit are also necessary to sustain the quality of the blood culture in the future.

MM8: Triazole resistance in Candida tropicalis: Are we in dire straits?

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Introduction: Candida tropicalis is a globally distributed yeast that is notorious for its association with substantial morbidity, mortality as well as drug resistance. The aim of this study was to ascertain the triazole susceptibility profile of this notorious yeast in our medical centre. *Materials & Methods: C. tropicalis* isolates from sterile specimens were collected over a 12-month period. Conclusive identification was achieved biochemically with the ID 32C kit. Susceptibility test to four triazole antifungal agents (i.e. fluconazole, itraconazole, voriconazole and posaconazole) was carried out using the colourimetric broth microdilution kit, Sensititre YeastOne YO10. The relevant Clinical & Laboratory Standards Institute documents were used to interpret the MIC readings. *Results:* Twenty-four non-repetitive isolates of *C. tropicalis* were collected. A total of 7/24 isolates were fluconazole-resistant, resulting in a fluconazole resistance rate of 29.2%. Voriconazole resistance was detected in 5/24 isolates (20.8%). Only 2/24 (8.3%) isolates were resistant to posaconazole. Lastly, for itraconazole, 4/24 (16.7%) of our isolates tested resistant. Resistance to all four triazoles tested was observed in two isolates (8.3%). Coincidentally, these two isolates were also posaconazole-resistant. *Discussion:* The *C. tropicalis* isolates from our centre have the highest resistance rate to fluconazole and the lowest to posaconazole. While these data have yet to put us in dire straits, the very fact that triazole resistance (even to higher generation triazoles) has already been documented means that we cannot afford to be complacent.

MM9: T-cell response to a single dose of BNT162b2, CoronaVac, and ChAdOx1 vaccines in COVID-19 naïve subjects

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Introduction: COVID-19 immunity is crucial for preventing and mitigating morbidity and mortality. Several COVID-19 vaccines have been used in Malaysia, including BNT162b2 (Pfizer-BioNTech), CoronaVac (Sinovac), and ChAdOx1 (Oxford-AstraZeneca). Antibody production in the context of vaccine-induced protection has been the focus of interest; however, the cellular immune response also needs to be emphasised. Therefore, we examined the T-cell response elicited after a single dose of BNT162b2, CoronaVac, or ChAdOx1 in COVID-19 naïve subjects. *Materials and Methods:* We assessed the T-cell immune response in cryopreserved peripheral blood mononuclear cells (PBMC) with an enzyme-linked immunospot (EliSpot) assay kit (Mabtech AB, Sweden). The PBMC were stimulated with SARS-CoV-2 spike-specific peptides and the interferon-gamma (IFN-γ) secreted cells were determined using IRIS Mabtech EliSpot plate reader. *Results:* This study involved 127 COVID-19 naïve subjects who received a dose of either BNT162b2, CoronaVac, or ChAdOx1. Blood was collected at the time point before the first and the second doses of the vaccine. All subjects had no reactive T-cell response at baseline. Before the second dose, 100% of BNT162b2 (43/43) and ChAdOx1 recipients (44/44) showed T-cell reactivity with a median of 184 (118-230) and 136 (88-184) spot-forming unit (SFU)/10^6 PBMC, respectively. For CoronaVac recipients, 90% (36/40) showed T-cell reactivity with the lowest median of 68 (40-117) SFU/10^6 PBMC. *Discussion:* The results demonstrated that all vaccines studied could prime the T-cell immune response in COVID-19 naïve subjects. Activation of the T-cell response by COVID-19 vaccination contributes to the reduction of disease severity and transmission of the virus.

MM11: A reference laboratory experience on molecular approach to *Streptococcus pneumoniae* serotyping in adult Malaysian samples.

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Introduction: Epidemiological data of capsular serotypes of *Streptococcus pneumoniae (S. pneumoniae)* from patient specimens with invasive infection provide a valuable insight in disease control measures. Even though the organism is identifiable in two-third of cases, a small proportion were unable to be serotyped by gold-standard Quellung reactions due to autoagglutination and/or unavailability of specific antisera. We aimed to evaluate the application of molecular methods for *S. pneumoniae* serotyping. *Materials & Methods:* A total of 43 out of 621 isolates demonstrating autoagglutination using Quellung reactions received from various hospitals between 2020 to 2022, were selected for molecular serotyping. Briefly, extracted DNA from pure colonies was subjected to molecular assay protocol comprising conventional multiplex PCR with/without real-time PCR. Confirmation of serotypes was achieved by DNA sequencing of the amplified product of the target. Concurrently, identity of *S. pneumoniae* was confirmed using *cps*A gene via conventional PCR. *Results*: Out of 43(6.9%) isolates exhibit autoagglutination using Quellung reactions, 32 (74.4%) isolates were successfully serotyped using the molecular method; majority were serotypes 6A/6B, 19A, 19F and 34 (n= 24, 55.8%). Some serotypes were undifferentiable and reported as 6A/6B (n=6, 13.9%) and 6C/6D (n=3, 7.0%) due to high similarity in DNA sequence. Interestingly, dual-serotypes were also observed in two isolates (4.7%) (serotypes 19A and 19 F, 19A and 6A/6B). However, 11 (25.6%) isolates remained non-typable. *Discussion:* Limitation of conventional Quellung reactions for *S. pneumoniae* serotyping can be resolved by application of molecular techniques. Nonetheless further optimisation is required in the near future.

MM12: Trimethoprim-sulfamethoxazole resistance in *Burkholderia pseudomallei* ST289 causing Spinal Melioidosis: A case report

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Introduction: Melioidosis is a bacterial disease caused by *Burkholderia pseudomallei*. The infection presents a wide clinical spectrum, but involvement of the spine is a rare phenomenon. High clinical suspicion, prompt diagnosis may avoid harmful consequences of the disease. *Case report:* A 12-year-old girl with underlying systemic lupus erythematosus (SLE) presented with fever and was diagnosed with systemic melioidosis infection from positive blood culture. She still experienced intermittent fever and started having back pain despite treatment for 3 months. A lumbosacral magnetic resonance imaging revealed a pathological fracture of L3 lumbar spine with intraosseous abscess. A computed tomography-guided drainage of the collection was performed, and the pus aspirate tested positive for *Burkholderia pseudomallei* DNA using polymerase-chain reaction. Subsequently, a colony was isolated from the pus and identified as *Burkholderia pseudomallei* using mass spectrometry. The isolate was susceptible to amoxicillin-clavulanate, imipenem, ceftazidime, doxycycline, but resistant to tetracycline and trimethoprim-sulfamethoxazole. Further whole genome analysis resulted with ST289 and several resistant gene mutations. She is currently undergoing treatment, to complete 12 weeks intravenous meropenem and 6 months of eradication therapy. Subsequent repeated MRI showed improvement in the degree of inflammatory changes seen over the abscess's region. *Discussion:* Drug-resistant *B. pseudomallei* can cause failure in treatment. Melioidosis of the spine is rare and immunosuppressive patients are at risk. Good awareness and availability of relevant laboratory tests in predicting drug-resistant strain are critical in avoiding fatal consequences of drug-resistant *B. pseudomallei* spinal infection especially in immunocompromised patients.

MM13: A case of neuromelioidosis in a young immunocompetent patient

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Introduction: Neuromelioidosis is a rare and severe manifestation of melioidosis caused by *Burkholderia pseudomallei*, primarily affecting individuals living in endemic regions. This report describes a case of neuromelioidosis, particularly in a young patient. *Case report*: A 17-year-old male with no comorbidities was brought to the Emergency Department with altered consciousness, a 12-day fever, and a cough. Physical examinations revealed a low Glascow Coma Scale of E2V1M3, hypoxia, and bilateral pulmonary crepitation, requiring ventilation support. He was diagnosed with community-acquired pneumonia with septic encephalopathy. Extensive radiological studies, including brain MRI, later revealed multiple brain abscesses with pansinusitis and bilateral mastoiditis. The brain abscesses were surgically drained, and the abscesses were sent to the microbiology laboratory for culture and sensitivity testing. Additional samples sent for culture and sensitivity testing including blood and tracheal aspirate. However, only cultures from the brain abscess yielded a significant pathogen reported as *Burkholderia pseudomallei*. Hence, the diagnosis of neuromelioidosis was established. Despite the interventions, the patient's condition continued to deteriorate, eventually leading to his death. *Discussion*: Neuromelioidosis primarily affects immunocompromised individuals, such as those with diabetes or kidney disease. However, in this report, the risk factors were noticeably absent except for the geographical factor. Nevertheless, neuromelioidosis has been reported to affect young and healthy individuals. Neuromelioidosis in young patients is particularly concerning due to poor outcomes, with a higher incidence of severe sepsis and neurological impairment leading to increased mortality rates. The mortality rate for neuromelioidosis is approximately 30%, and around 50% of patients experience residual neurological deficits.

MM14: Lethal multidrug resistant *Trichosporon asahii* in an immunocompromised patient: A case report

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Introduction: Trichosporon asahii is an emerging fungal pathogen associated with immunosuppressed patients, including those with haematological malignancies and recently with COVID-19 co-infection. As reported by Li H et al, *T. asahii* infection exhibits mortality rate with a range of 53% to 80% and poses a great risk to patients subjected to potent immunosuppressive agents or immunocompromised individuals. *T. asahii* tends to display high MIC value towards commonly employed empirical antifungal agents, such as amphotericin B, fluconazole and echinocandins. However, this pathogen exhibits good susceptibility to voriconazole. *Case report:* In this case study, we delved into the extraordinary journey of a 74-years-old patient with an extended hospitalisation and ICU stay, central venous catheter placement, and treatment with broad-spectrum antibiotics. Blood culture from a peripheral blood sample yielded dry and fuzzy, white colonies on Sabouraud dextrose agar. Lactophenol Cotton Blue (LPCB) stain showed finding of yeast-like blastoconidia with barrel-shaped arthroconidia and later confirmed by API 32C with %ID of 99.9, 6 days after obtaining blood culture. Nevertheless, the antifungal sensitivity test was not conducted owing to the absence of Clinical and Laboratory Standards Institute (CLSI) breakpoint parameters. Patient received antifungal treatment regimen comprising 6 days of IV fluconazole and later changed to IV voriconazole based on

the final report, for 17 days until the patient succumbed to his multiple concurrent infection including the multidrug-resistant *Acinetobacter* spp. ventilator-associated pneumonia. *Discussion:* Prompt diagnosis and initiation of appropriate antifungal therapy are crucial in immunosuppressed individuals. In some cases, presumptive identification by LPCB stain may facilitate the initiation of appropriate antifungal choice.

MM15: A case report of histoplasmosis presenting as left cervical neck abscess with lymphadenopathy

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Introduction: Histoplasmosis is a mycotic infection caused by dimorphic fungi *Histoplasma capsulatum* that has been most frequently reported as opportunistic fungal infections, particularly in immunocompromised patients. Classical histoplasmosis typically presents as pulmonary infection, mediastinal fibrosis, and mucocutaneous lesion but rarely as a neck mass. We described a case of left cervical neck abscess with lymphadenopathy in a newly diagnosed Human Immunodeficiency Virus (HIV) and Hepatitis B. *Case Report*: A 24-year-old male with no known medical history, presented with progressively enlarged left neck swelling associated with fever, hoarseness of voice and loss of weight for two weeks. Upon examination, a firm and tender palpable mass measuring 5cm x 5cm was located at the anterior border of the left sternocleidomastoid. Contrast-enhanced computed tomography (CECT) of the neck showed a multiloculated left cervical collection causing almost the entire compression of the left internal jugular vein (IJV) with cervical lymphadenopathy. An emergency operation was performed and intraoperative findings revealed a deep abscess with multiple necrotic and enlarged nodes at level II and III. Pus aspirate and lymph node tissue were negative for acid-fast bacilli (AFB) stain. Fungal culture showed growth of *H.capsulatum,* identified from colony appearance and lactophenol cotton blue stain (LPCB). Histopathological finding of the lymph node demonstrated necrotising granulomatous lymphadenitis with presence of fungal organism, morphologically suggestive of histoplasmosis. Patient subsequently tested positive for hepatitis B and stage 3 HIV with a total $CD4^+$ lymphocyte count of 108 cells/μL. The patient was diagnosed with histoplasmosis of the cervical lymph node and was treated with oral itraconazole and Highly Active Antiretroviral Therapy (HAART). His symptoms resolved and recovered well. *Discussion*: Histoplasmosis presenting as a neck mass is diagnostically challenging because of its rare presentation. The symptoms of disseminated histoplasmosis are non-specific and this may be indistinguishable from other infectious diseases, especially disseminated tuberculosis. Due to varied and nonspecific clinical manifestations of histoplasmosis and low index of suspicion, most of the infections were misdiagnosed or underreported. Despite diagnostic challenges of *H.capsulatum* with other various opportunistic pathogens, microbiology diagnostic laboratories are able to identify the aetiological agent with supportive evidence from histological findings to provide a correct diagnosis.

MM16: Predominance of SCC*mec* type IV in community and hospital acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in tertiary Malaysian hospitals

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Introduction: Hospital epidemiology of MRSA has changed in the past few years due to the emergence of community-acquired MRSA isolates. To date, these community-genotype (CG)-MRSA clones have overtaken hospital-genotype (HG)-MRSA. The increasing number of infections caused by CG-MRSA in healthcare associated infections are very concerning. To determine the magnitude of this hypothesis in Malaysian settings, molecular characterisation of local community-acquired (CA)-MRSA and hospital-acquired (HA)-MRSA strains was carried out to assist clinicians in determining the most optimal treatment and management. *Materials & Methods:* A total of 549 clinical MRSA isolates were collected from two tertiary hospitals in Klang Valley between June 2020 to June 2022. SCC*mec* and virulence genes were detected using multiplex PCR. *Results:* Seventy-five percent of the isolates harboured SCC*mec* type IV. Majority of isolates were from patients admitted into the medical department (n=221) and isolated from blood specimens (n= 131). *hl*α was detected in 95% while *pvl* was detected in 12% of the isolates. All isolates conferred resistance to cefoxitin and none of them were resistant to vancomycin. *Discussion:* Although SCC*mec* type IV was prominently reported in CA-MRSA previously, our study, however, found SCC*mec* type IV to be predominant in both CA-MRSA (71%) and HA-MRSA (77%) isolates. *pvl,* which was used to be associated with CA-MRSA, was detected only in a small number of CA-MRSA isolates which is in accordance with other recent studies. Our findings provide insightful information on the genotyping of CA and HA-MRSA isolates circulated in Klang Valley, providing crucial baseline information for future research and surveillance purposes.

MM17: Diabetes mellitus correlation with nontuberculous Mycobacterium disease: A narrative review of clinical case studies

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Introduction: Diabetes mellitus (DM) is a common endocrine disorder that is linked to oxidative stress, immune dysfunction, and inflammatory changes that increase susceptibility to infections, including nontuberculous mycobacterium (NTM), which is an opportunistic pathogen found in various environments. However, the association between DM and NTM infections

has not been extensively studied. This narrative review explores the correlation between DM and NTM disease through an analysis of clinical case studies. *Materials and Methods:* A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Cochrane, POPLINE, Google Scholar, and Scopus, for all articles published up to March 2023 on the NTM and DM. A total of 47 studies were returned, and only 26 studies were included based on eligibility criteria. The inclusion criteria are patients with DM with confirmed NTM infection and complete English-language articles, including case reports, case series, letters to the editor, and case presentations. Exclusion criteria are duplicate cases, comorbidities other than DM, narrative review and systematic review articles, and articles without full text. *Results:* Type 2 DM accounts for 75% of the 26 cases. At the time of infection, 12 individuals had high HbA1C levels that were reported. The most frequently isolated NTM species were *Mycobacterium fortuitum* and *Mycobacterium chelonae*. The most frequent manifestation of NTM infections is skin lesions, followed by lung infections, osteomyelitis, and bloodstream infections. *Discussion:* Hyperglycaemia, a hallmark of DM, contributes to the impairment of the immune response through reduced phagocytosis and bactericidal activity, thus increasing vulnerability to infection by NTM. However, the exact mechanisms underlying the association between DM and NTM disease require further investigation.

MM18: Performance of rapid antigen assay for SARS-CoV-2 genomic surveillance: A cross-sectional study

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Introduction: Genomic surveillance aimed to ensure an effective response to a novel emerging SARS-CoV-2 variant. During the earlier days of the pandemic, diagnostic rtPCR samples were a known primary specimen used for sequencing. The recent transition into the endemic phase has seen a tremendous reduction in the number of rtPCR conducted with increased utilization of rapid antigen assay. This study provides insights into the utilisation of residual buffer-sample mixture (RBSM) of the COVID-19 antigen rapid test kit (Ag-FIA) as the primary source for whole genome sequencing (WGS). *Materials & Methods:* Nasopharyngeal swabs were collected from October 2022 to April 2023 from a teaching hospital in Pahang. Ag-FIA was conducted on all samples. By using the RBSM of the positive Ag-FIA, RNA extraction and SARS-CoV-2 rtPCR was conducted. Samples with cycle threshold (ct) value of less than 30 (sequencing criteria) were subjected to WGS. Data analysis was performed using GISAID. *Results:* A total of 12059 swabs were collected. Ag-FIA positivity rate was at 2.7% (321/12059). Upon rtPCR, 224/321 (69.8%) samples fulfill the sequencing criteria with an average Ag-FIA cutoff index of 76.8. To date, 66 samples were completely sequenced where 45.5 % (30/66) produced a valid result. They all belong to a single Omicron lineage B.1.1.529. *Discussion:* This study demonstrates that the RBSM from Ag-FIA can generate a substantial number of valid sequencing results. A standardised protocol needs to be established to further optimize COVID-19 rapid antigen assay as the primary source for sequencing. Such a measure is crucial to encourage local and global participation in SARS-CoV-2 genomic surveillance.

MM19: Ceftazidime/avibactam and ceftolozane/tazobactam activity against *Pseudomonas aeruginosa*: single-site insights from the SMART study

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Introduction: Multidrug-resistant *Pseudomonas aeruginosa* represents an increasingly significant healthcare challenge. This site-specific investigation, part of the Study for Monitoring Antimicrobial Resistance Trends (SMART), evaluated the activity of ceftazidime/avibactam (C/A) and ceftolozane/tazobactam (C/T) against *P. aeruginosa* isolated from a Malaysian tertiary hospital. *Materials & Methods*: From 2017-2021, clinically-relevant *P. aeruginosa* isolated from various sources were submitted to a central laboratory (IHMA, USA) for antimicrobial susceptibility testing. Minimum inhibitory concentrations were determined using broth microdilution, interpreted per CLSI breakpoints. *Results*: Overall, 208 *P. aeruginosa* isolates (67 ICU, 141 non-ICU) were evaluated. C/T susceptibility was tested from 2017-2021 (n=208), whereas C/A was tested from 2018 onwards (n=170). Respiratory tract infections comprised 59%, followed by urinary (16.4%), intra-abdominal (16.4%), and bloodstream infections (8.2%). C/A and C/T were active against 94.1% and 92.3% of isolates, surpassing most β-lactam comparators by 5-10 and 3-8 percentage points, respectively. ICU isolates displayed 96.6% and 94% susceptibility towards C/A and C/T, compared to 92.8% and 91.5% from non-ICU. Among subsets non-susceptible to ceftazidime, cefepime, or piperacillin-tazobactam, C/A and C/T showed activity against 59.4% and 51.2%. Importantly, C/A and C/T remained active against 48% and 40.6% of carbapenem-resistant isolates, respectively. *Discussion*: C/A and C/T demonstrated greater activity against *P. aeruginosa* in comparison to traditional antibiotics, including carbapenem-resistant strains. Interestingly, our ICU isolates were more susceptible than their non-ICU counterparts, albeit with smaller sample size. Notably, C/A and C/T maintained efficacy against almost half of carbapenem-resistant *P. aeruginosa* isolates, suggesting their potential role in therapeutic strategies across ICU and non-ICU settings.

MM20: Development and evaluation of a real-time PCR assay targeting the DNA-binding transcriptional regulator family of *Burkholderia pseudomallei*

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Introduction: Melioidosis, a potentially fatal disease caused by *Burkholderia pseudomallei* is an endemic disease in Malaysia. This study aimed to develop a real-time PCR (RT-PCR) assay to identify and distinguish *Burkholderia pseudomallei* from other bacterial isolates. The assay targets a 171-base-pair region of the *B. pseudomallei* DNA-binding transcriptional regulator family. *Materials & Methods:* A total of 30 bacterial isolates were screened including 25 *B. pseudomallei* isolates and 5 other bacterial isolates (*Pseudomonas aeruginosa, Burkholderia cenocepacia, Klebsiella pneumoniae, Enterococucus faecalis*). The bacterial was identified and confirmed by biochemical tests and whole genome sequencing. The bacterial DNA was extracted and subjected to an in-house optimized protocol of SYBR Green RT-PCR run using primers targeting BPS3X2 and *16S rRNA*. *Results:* BPS3X2 is able to differentiate *B. pseudomallei* from the other bacterial isolates, at early PCR cycle thresholds (14 to 20). The results were comparable with *B. pseudomallei*-specific *16S rRNA*, a commonly-used reference gene with cycle thresholds (12 to 18). This assay using BPS3X2 primers demonstrated a PCR efficiency value at E=1.02 and regression coefficient, R^2 =0.99. *Discussion:* This assay targeting *BPS3X2* gene performed with 100% specificity to distinguish *B. pseudomallei* from other bacteria. The assay could detect as few as 0.1 pg of DNA in a single PCR. Further evaluation in clinical samples and more bacterial isolates will be required to further improve the precision of the assay. Nevertheless, this rapid assay could serve as a valuable tool for *B. pseudomallei* identification especially in melioidosis-endemic countries.

MM21: Detection of respiratory pathogens with automated multiplex PCR in a tertiary medical centre in Kuala Lumpur

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Introduction: Respiratory viral infections pose a significant global health burden. We analysed a dataset comprising samples collected between September 2022 and July 2023 using automated multiplex PCR test. *Materials & Methods*: A total of 912 nasopharyngeal swabs in UTM were received and tested using the QiaStat Multiplex SARS-CoV-2 Respiratory Panel. *Results*: The overall detection rate of respiratory viruses was 78.84%. Rhinovirus/Enterovirus had the highest detection rate at 42.76%, followed by RSV A+B at 18.53%, and Adenovirus at 8.66%. Influenza A (Flu A) was detected in 6.25% of samples, while Influenza A subtypes (H1N1 pdm09 and H3) and Influenza B were found at 4.06%, 2.08%, and 2.30%, respectively. Parainfluenza viruses 1 to 3 displayed varying detection rates ranging from 1.32% to 3.40%, while the remaining viruses or pathogens had lower or zero detection rates. *Discussion:* The high overall detection rate highlights the substantial burden of respiratory viral infections in the studied population. Rhinovirus/enterovirus, with the highest detection rate, is known for its broad clinical manifestations and year-round circulation. RSV A+B and adenovirus emerged as significant respiratory pathogens, indicating seasonal variation and emphasizing the need for targeted interventions during peak seasons. The relatively lower detection rate of SARS-CoV-2 may be attributed to vaccination efforts and public health measures aimed at controlling its spread. These findings provide insights into the diversity and distribution of respiratory viruses pathogens, aiding in diagnostic and surveillance efforts to facilitate effective management and control measures.

MM22: The cyp51A mutations of clinical *Aspergillus fumigatus* in Malaysia

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Introduction: Aspergillus fumigatus is a significant fungal pathogen responsible for invasive aspergillosis, and the emergence of azole resistance poses challenges in its management. The *cyp51A* gene mutations have been identified as key contributors to azole resistance in *A. fumigatus*. This study aimed to investigate the *cyp51A* mutation profiles of clinical *A. fumigatus* isolates in Malaysia. *Materials & Methods:* A total of 60 clinical *A. fumigatus* isolates collected between 2019 and 2023 were included in the analysis. PCR primers, namely Cyp51A_1 and Cyp51A_2, were designed to detect gene mutations in the *cyp51A* gene. The PCR products were subsequently subjected to Sanger sequencing, and the obtained sequences were compared to the wild-type A. *fumigatus CYP51A* reference sequence. *Results:* Among the 60 isolates, 47 showed no mutations, while 13 isolates exhibited mutations in the *cyp51A* gene. The identified mutations included E427K, F46Y, N248K, R34L, V244S, V244A, and M172V. *Discussion:* While these point mutations alone did not solely account for azole resistance, our findings partially supported the claim that the N248K mutation might compromise the efficacy of azole therapy. Notably, the commonly reported mutations, such as TR34/L98, G54, M220, and G448, were not observed in this study. This highlights the potential unique genetic diversity and distribution of *cyp51A* mutations in *A. fumigatus* among different geographic regions and populations. Further research is needed to explore the clinical implications of these mutations and their association with azole resistance for better management of invasive aspergillosis.

MM23: Port of trouble: *Kodamaea ohmeri* as an unusual culprit in catheter-related bloodstream infection in an acute myeloid leukaemia patient

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Introduction: Kodamaea ohmeri, a rare yeast, has been increasingly implicated in infections among immunocompromised patients. We present a unique case of catheter-related bloodstream infection (CRBSI) caused by *K. ohmeri* in a patient with acute myeloid leukaemia (AML). *Case report:* A 45-year-old woman with AML, on day 9 of chemotherapy, developed a febrile episode two days post-admission, following a packed cell transfusion. Blood cultures from her chemoport and peripheral sites (flagged more than 2 hours apart) demonstrated budding yeast cells. Identified via MALDI-ToF mass spectrometry as *K. ohmeri*, the initially indistinguishable white yeast colonies transformed into the characteristic pink-blue hues after 48 hours. Given potential fluconazole resistance (MIC 8 µg/ml), the patient was initiated on Amphotericin B and voriconazole, and her chemoport was promptly removed. The fungemia resolved within a week, leading to an uncomplicated recovery. *Discussion:* Our case highlights the importance of early recognition and targeted management of CRBSIs caused by uncommon pathogens like *K. ohmeri*. The timing of symptom onset and ongoing chemotherapy suggest potential colonisation of the chemoport during treatment, emphasising the need for meticulous port care. Timely and highly-specific diagnostic methods, such as MALDI-ToF, played a crucial role in identifying *K. ohmeri* in this case, surpassing slower conventional methods. Although our patient did not exhibit overt sepsis symptoms, the decision to remove her chemoport likely contributed to the favourable outcome. Notably, the relatively high fluconazole MIC and current lack of established antifungal breakpoints for *K. ohmeri* underscore the need for further research to optimise treatment strategies.

MM24: Group B *streptococcus* bacteremia, infective endocarditis and polyarticular septic arthritis in a non-pregnant adult

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Introduction: Streptococcus agalactiae (GBS) is a colonizer of the genitourinary tract in up to 30% of humans. The greatest burden of disease from GBS falls on pregnant women and neonates, with it being the most common cause of neonatal bacteraemia, meningitis, and pneumonia worldwide. However, evidence suggests a shift in GBS infections, with non-pregnant adults experiencing invasive cases from 1.50 cases (1975-1995) to 3.79 cases per 100,000 (2006-2018). Invasive GBS can affect any organ system and accounts for a small fraction of infective endocarditis, a potentially fatal condition. *Case report:* We present a case of bacteraemia in a previously healthy 55-year-old non-pregnant lady and possible source from oral cavity with poor hygiene. Despite having no typical risk factors of invasive GBS, the clinical presentation was polyarticular septic arthritis involving the left knee, right ankle, right wrist with right hand abscess, whereby GBS was isolated from synovial fluid and tissue culture of the wrist and knee. The patient also developed a mild form of infective endocarditis, in which vegetation was seen on her mitral valve on transthoracic and transoesophageal echocardiogram with one positive blood culture for GBS. She achieved full recovery after arthrotomy washout and completion of intravenous benzylpenicillin antibiotic therapy. *Discussion:* Oral cavity colonisation by GBS, consequently causing bacteraemia, is relatively uncommon compared to other *Streptococci* within the Viridans group but it may be possible as presented in this case. Therefore, emphasis on oral hygiene is still among the important measures in preventing infective endocarditis, especially in high-risk patients.

MM25: The adaptive mutational profiles of Malaysian SARS-CoV-2 virus in clinically important mammalian cell lines

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Introduction: Since its first emergence in 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has continued to spread all over the world. Virus propagation is essential to generate stocks for various kinds of investigations. However, mounting evidence has shown that *in vitro* propagation of SARS-CoV-2 have resulted in acquired mutations due to adaptation. *Materials & Methods:* Three (3) local SARS-CoV-2 isolates, i.e. clades L/Lineage B Wuhan (WC1114/20), GR/Lineage B.1.1.354 (WI119/20), and O/Lineage B.6.2 (WC81849) were adapted into Vero E6, Vero-CCL-81, Calu-3, MRC-5, and A549. Adaptation mutation was determined by comparing the single nucleotide polymorphism (SNP) in these viruses between passages. SNPs were identified by whole genome sequencing (WGS) *Results:* Except for WC1114/20 isolate adapted in CCL-81, SNPs occur in all isolates after adaptation into all cell lines used in this study. The SNPs occur more often in the spike glycoprotein in comparison to membrane glycoprotein and nucleocapsid. Adaptive mutations acquired by the isolates were distinguishable among the cell lines, with MRC-5 recorded the greatest number of SNPs. Important mutations such as D614G was mostly retained in these cell lines. *Discussion:* This study provides the information on the SNP and mutational profiles of local SARS-CoV-2 virus after serial passages *in vitro*. Besides providing the list of mutations acquired during the adaptation, our study also postulates the cell lines that will conserve the important mutations in SARS-CoV-2 such as D614G.

MM26: *Salmonella enterica* serotype Agona in infant with meningitis and cerebral abscess

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Introduction: Salmonella meningitis is an uncommon form of intracranial infection, particularly in infants. It remains a threat with severe complications. *Case report:* A 6-month-old girl presented with fever, vomiting and seizure. Due to impending status epilepticus, she was intubated and empirically treated for meningoencephalitis. The patient had no sick contact but started consuming formula milk in addition to breastfeeding before the onset of symptoms. Neurological examination revealed hypertonia of all four limbs and the contrast CT brain reported as asymmetrical bilateral thalamic changes, white matter lesion and cerebral oedema. Her blood and cerebrospinal fluid cultures yielded gram negative rod, non-fermenter organism with abundant hydrogen sulphide, positive for O and H antigen but negative for Vi antigen. Vitek 2.0 (BioMérieux, USA) named the organism as *Salmonella spp*. The serotyping test (Bio-Rad, USA) revealed *Salmonella enterica* serotype Agona. The organism was resistant to ampicillin, susceptible to amoxicillin-clavulanate, ceftriaxone and ciprofloxacin. Despite seven days on intravenous ceftriaxone, the patient had persistent temperature and MRI brain showed bilateral deep grey and white matter abscess and frontotemporal empyema. The patient's condition was improved after 4 weeks of intravenous ceftriaxone and 3 weeks of intravenous ciprofloxacin before being transferred to another hospital. The antimicrobial was continued for another 3 weeks before being discharged home. *Discussion: Salmonella spp*. infection has been linked to contaminated breast milk. *Salmonella* Agona can survive powdered milk products up to 180 days. Multiple outbreaks of *Salmonella* Agona in infant milk products had been reported in France. The knowledge on proper milk storage and handling can reduce risk of infection.

MM27: A rare case of infective endocarditis caused by *cfiA*-positive *Bacteroides fragilis*

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Introduction: Bacteroides fragilis is an anaerobic gram-negative bacillus that is part of the normal flora in the human gastrointestinal tract. Anaerobic bacteria are an uncommon but important cause of infective endocarditis, which accounts for 2–16% of all cases. We report here a case of infective endocarditis caused by a rare multidrug-resistant strain of *Bacteroides fragilis*. *Case report:* A 58-year-old lady with underlying end-stage renal failure presented with a sudden onset of left-sided body weakness, facial asymmetry, and slurred speech. Plain CT-brain showed multifocal acute infarcts and subsequently, a transthoracic echocardiogram revealed vegetation measuring 0.95cm by 0.52 cm over the lateral tricuspid annular. She was empirically started on intravenous cefazolin and ampicillin-sulbactam. However, no growth was obtained from the three sets of blood cultures taken upon admission. A fourth set of blood cultures was taken as her condition was not improving. The anaerobe blood culture was positive for gram-negative bacilli. The isolate was identified by MALDI-TOF MS as *cfiA*-positive *Bacteroides fragilis*. Antibiotic susceptibility testing using E-test showed resistance to amoxicillin-clavulanic acid (>256 µg/ml), ceftriaxone (>256µg/ml), imipenem (>32 µg/ml), piperacillin-tazobactam (>256 µg/ml) and meropenem (>32 µg/ml). Her condition deteriorated and she passed away due to infective endocarditis with cerebral infarction. *Discussion:* A higher mortality rate among patients with anaerobic infective endocarditis can be due to the delay in diagnosis. In addition, the absence of effective antibiotic in this patient further contributed to poor prognosis. Utilisation of MALDI-TOF MS in rapid identification of cfiA-positive strain is useful in directing patients management to reduce morbidity and mortality.

MM28: Fatal disseminated melioidosis in an unlucky middle-aged lady due to delay in diagnosis

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Introduction: In Malaysia, Melioidosis is not a notifiable disease but has a very high mortality rate, especially in diabetic patients. The disseminated case is potentially fatal. About 16–37% of cases, present with indefinite presentation, and some with clinical signs of abscess formation in multiple organs with or without bacteraemia. We report a fatal case of disseminated melioidosis in diabetic patients due to a delay in diagnosis. *Case report:* 49 years old lady with underlying diabetes mellitus with diabetic foot ulcer presented with a disseminated melioidosis clinical manifestation with the initial presentation was a history of dyspnoea later on, developed abdominal pain and persistent fever, and subsequently went into septicaemia. She was initially misdiagnosed as NSTEMI, chest x-ray showed a fluid overload picture and due to the low septic parameter, no antibiotic was prescribed. Later on, she was empirically covered with intravenous ceftriaxone and intravenous metronidazole for almost 5 days for acalculous cholecystitis based on ultrasound abdomen and Contrast Enhanced CT scan (CECT) results at that time. However, no sonographic evidence of gallbladder empyema. Diagnosis of septic shock secondary to disseminated melioidosis was only made later after observation of laboratory findings and her condition deteriorated further on day 10 of admission developing septic shock, acute kidney injury, coagulopathy, and transaminitis and required intubation. Repeated Chest x-ray shows worsening pulmonary infiltrate. The treatment was upgraded to intravenous meropenem. However, the patient succumbed after 16th day of hospitalization. *Discussion:* Diagnostic challenge in this patient was that there is no pathognomonic presentation in Melioidosis. The diagnosis of Melioidosis was not apparent in this patient until the blood culture and sensitivity show a Gram-negative rod and the final results show *B.pseudomallei*. She has very vague symptoms that initially were misdiagnosed with the addition of the initial culture being negative which further caused delays in diagnosis.

Blood culture is the gold standard in the diagnosis and the serological method was helpful but with some limitations. This case study emphasizes the significance of taking melioidosis into account in Malaysian high-risk populations for early diagnosis and treatment.

MM29: Mothers with anti-Ro autoantibodies and the risks of congenital heart block to their offspring: A case series

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Introduction: Congenital heart block (CHB) following maternal anti-Ro/La autoantibodies is a serious complication of neonatal lupus with a prevalence of 1:22000 live birth. It is associated with high morbidity and mortality. Disturbance of calcium homeostasis which leads to electrical conduction abnormality and fibrosis of the heart tissue is the well-known pathogenesis of CHB. Most of the newborns with CHB ended up with a third-degree heart block requiring a pacemaker as it is an irreversible injury. *Case series*: We present four cases of neonatal lupus with cardiac manifestation necessitating a permanent pacemaker (PPM) by the latest age of two months in infants born to mothers with positive anti-Ro/La autoantibodies. All cases presented with foetal bradycardia and were detected between 24 to 32 weeks of gestation. Three CHB cases had no maternal connective tissue disease (CTD) history, and anti-Ro/La screening was only performed after the echocardiography findings. In the fourth case, treatment was administered early before conception since the mother is known to have anti-Ro/La seropositive SLE. However, the infant developed severe CHB despite early intervention, necessitating PPM on the first day of life. *Discussion*: Incorporating the anti-Ro/La testing into antenatal workup can serve as an early screening for all asymptomatic pregnant women, regardless of their CTD history. This will provide better outcomes for the offspring at risk through foetal echocardiogram surveillance and prompt treatment. Anti-Ro titres and additional autoantibodies, including anti-La can predict the severity of CHB. Identifying other autoantibodies and genetic diversity could also assist clinicians in managing CHB.

MM30: Fatal outcome of healthcare-associated infective endocarditis (HCA-IE) by S*taphylococcus lugdunensis*: Rare but not to be missed

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Introduction: Evolution of invasive therapeutic and diagnostic procedures has resulted in an increasing incidence rate of healthcare-associated infective endocarditis (HCA-IE). *Staphylococcus lugdunensis* infective endocarditis is infrequently reported, but is recognised as the pathogen for infective endocarditis (IE) due to its ability to form biofilm on the prosthetic devices or intravascular catheter. *Case report:* A 58 years old man presented with fever for one day and was less responsive. He is a known case of end stage renal disease and on regular haemodialysis via right internal jugular catheter (IJC) inserted five months ago. Upon arrival the patient was afebrile, tachycardia with moderate Glasgow coma scale (GCS). Cardiovascular examination revealed loud pansystolic murmur best heard over mitral area and transthoracic echocardiogram (TTE) showed large regurgitation over anterior mitral valve suggestive of infective endocarditis. Blood investigation showed leukocytosis, predominantly neutrophil and high C-reactive protein. Two sets of blood culture grew *Staphylococcus lugdunensis* that was susceptible to cloxacillin. He was started on intravenous cloxacillin 2g QID. Patient deteriorated after two days of admission and his condition did not improve despite optimum therapy given. He died after twenty days of treatment due to septic shock secondary to mitral valve IE with septic encephalopathy. *Discussion*: *Staphylococcus lugdunensis* is an aggressive pathogen causing destructive IE in immunocompromised patients. As this patient is on regular haemodialysis, infection may begin with colonization of the IJC subsequently resulting in bacteraemia. Rapid diagnostic tool using MALDI-TOF reduces the timing of pathogen identification thus allowing early initiation of antimicrobial therapy. Appropriate antibiotic therapy reduces morbidity and mortality however he died due to severe complications of sepsis and encephalopathy.

MM31: The HLA-B*27 genotype landscape of anterior uveitis in Malaysia

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Introduction: Inflammatory eye disease can manifest as uveitis, an inflammation that occurs in the middle layer of the eye. Approximately 90% of patients presented with anterior uveitis, the most common form of uveitis in HLA-B*27-associated disease. In this study, we describe the HLA-B*27 positivity in patients presenting with anterior uveitis at eye clinics from all over Malaysia for three consecutive years. *Materials & Methods:* Data were collected retrospectively from 136 referral cases from the eye clinics to our institution from January 2020 until December 2022. DNAs were extracted from the patients' whole blood and were genotyped for the HLA-B locus by performing polymerase chain reaction and sequence-specific oligonucleotide probe hybridization (PCR-SSO) method. Descriptive statistics were applied. *Results:* The mean age of patients was 40.2 (SD 15.9) years with a male-to-female ratio of 2:1. Of 136 patients, thirty-six (26.5%) were genotyped as positive for HLA-B*27. Our further analyses revealed that the HLA-B*27:04 (63.9%) were the most common alleles

of these patients, followed by HLA-B*27:05 (27.8%), and HLA-B*27:06 (8.3%). *Conclusion:* The current study indicates that approximately one-quarter of anterior uveitis patients in recent years presented with positive HLA-B*27. Screening for HLA-B*27 in an anterior uveitis patient provides additional diagnostic clues to investigate further for patients who may present with other features of systemic diseases. A detailed clinical history is warranted to determine any correlation between HLA-B*27 positive anterior uveitis with other systemic manifestations.

MM32: Revealing molecular insight S177Q mutant and wild type of Respiratory Syncytial Virus (RSV) G protein against 3D3 antibody via computational approaches

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Introduction: RSV is a leading cause of severe lower respiratory tract disease in vulnerable patients. Previous study showed that the S177Q mutant in RSV G protein's central conserved domain (CCD) potentially increases antigenicity and binds to antibodies, making it a potential vaccine target. However, there is a lack of understanding on the molecular interaction of S177Q mutant with the other monoclonal antibody (3D3). Therefore, this study aims to investigate the responses of S177Q mutant and wild-type CCD toward the 3D3 antibody by using computational approaches. *Materials & Methods:* Molecular modelling, molecular docking, molecular dynamics (MD) simulation, and antigenicity prediction were all applied. *Results & Discussion:* Molecular docking demonstrated that wild-type and mutant CCD were able to bind at 3D3 with -11.7 kcal/mol and -13.1 kcal/mol binding affinity, respectively. Further analysis using MD simulation revealed both simulations were stable for 100 ns with the wild-type had a lower RMSD (0.271 nm) compared to the mutant (0.388 nm). Meanwhile, MMPBSA analysis shows that wild-type binds strongly to 3D3 with an average of -62.16 kcal/mol and the mutant binds with -39.16 kcal/mol. Hydrogen bond and 2D analyses demonstrated that wild-type and mutant bind at the catalytic region of 3D3. However, wild-type has more interface residues and higher hydrogen bond occupancy compared to the mutant. Nevertheless, antigenicity prediction shows mutants have higher antigenic scores (0.7984) compared to wild-type (0.7459). *Conclusion:* Both wild-type and mutant are able to bind at 3D3 antibody, however, wild-type shows higher binding free energy with better interaction. The S177Q mutant demonstrated better antigenicity and in agreement with experimental findings.

MM33: Uncommon case of Shigella septicaemia: A case report

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Introduction: Shigella infection is usually manifested by acute gastroenteritis. It is uncommon that Shigella infection causes septicaemia. In this case report, we will present a case of Shigella septicaemia which may be caused by intra-abdominal infection after acute cholangitis. *Case report:* A 55 years-old male suffered from fever 40.3 Celsius degree, nausea, fatigue, and upper abdomen pain. He had a history of coronary heart disease s/p PCI 5 years ago. He also had a history of gallbladder stone and cholangitis. Physical exam found palpitation with 134 beats/minutes and right upper quadrant tenderness without Murphy's sign. Lab study found leukocytosis 19290/uL with CRP raised to 14.19 mg/dL. GOT, GPT, and total bilirubin were also elevated. Abdomen echo found dilated common bile duct. Microbiology studies found GNB from the patient's blood. MALDI-TOF suggested E. coli or Shigella species. Rapid biochemistry study was done and suggested Shigella infection. Under the impression of Shigella septicaemia, the patient received antibiotics treatment (Flumarin) and He underwent laparoscopic S6 segmentectomy, laparoscopic hepaticotomy and stone removal with cholangioscopy and laparoscopic cholecystectomy. He finally recovered and was discharged. *Discussion:* MALDI-TOF cannot successfully distinguish Shigella species and E. coli. In this case, we used a rapid chemistry test (API 20E) for identification. However, serotypes cannot be identified. The samples were sent to CDC for bacterial 16s ribosomal RNA for Shigella species identification. *Shigella flexneri* was identified. Whole genome sequencing could be the new technology for the identification. Shigella septicaemia is very uncommon. Host and environment can both contribute to the rare situation.

MM34: *Candida auris* causing urinary tract infection or rather a coloniser?

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Introduction: *Candida auris* is a rapidly emerging pathogen worldwide which may cause urinary tract infection or rather represent as a coloniser. *C. auris* causes severe infections and spreads easily between hospitalised patients, leading to outbreaks in hospitals. *Case report*: This is a case of a middle-aged diabetic and hypertensive gentleman with post bilateral below knee amputation (BKA) who presented with an infected left BKA stump. He underwent wound debridement of the infected stump where bone and tissue culture grew carbapenem-resistant *Enterobacterales* (CRE) *Escherichia coli*. The patient was treated with a two-weeks course of intravenous Piperacillin-tazobactam considering intra-operatively the wound and bone appeared clean and healthy. Later, derangement of renal profile was noted. His urine taken from the catheter grew mucoid whitish creamy colonies on Sabouraud Dextrose Agar (SDA). It was identified as *C. auris* by Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) with the score of 2.33 followed by confirmation using molecular identification. The

organism had elevated minimal inhibitory concentration (MIC) values to Fluconazole and Amphotericin B with low MIC of the Echinocandins. Subsequent urine cultures showed absence of *C. auris*. Hence, *C. auris* was regarded as a coloniser since there was absence of urinary tract infection symptoms along with renal profile improvement. Patient was discharged well. *Discussion*: *C. auris* is known to colonise or infect patients with risk factors such as significant medical comorbidities, urinary catheters and exposure to broad spectrum antibiotics as seen in this patient. Critical clinical decisions must be made in differentiating infection or colonisation prior to the commencement of antifungal and isolation.

MM35: Mucoid monster is the culprit: A case of community-acquired pyogenic liver abscess caused by hypervirulent *Klebsiella pneumoniae*

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Introduction: Community-acquired hypervirulent *Klebsiella pneumoniae* (hvKp) mainly colonize gastrointestinal tract and infect healthy individuals. The string test used formerly for its identification in clinical settings is less sensitive, prompting a need for novel biomarkers from virulence plasmids and chromosomal mobile genetic elements. *Case report:* A 50-year-old, previously healthy man presented with fever for a week, right upper quadrant abdominal pain, vomiting, diarrhoea and jaundice. Tenderness was elicited on superficial palpation of the right hypochondriac region, with no hepatomegaly. Infective markers showed leukocytosis and high C-reactive protein. Liver function test was deranged with conjugated hyperbilirubinemia, evidence of transaminitis and high alkaline phosphatase. Ultrasound abdomen revealed partially liquefied right liver abscess measuring 10.0cm x7.8cmx10.6cm. Blood culture was positive for Gram negative bacilli and identified as hypermucoviscous (positive string test) *Klebsiella pneumoniae*. Suspicion of hvKp was confirmed by polymerase chain reaction of the bacterial colony, which detected virulence genes *iroD*, *rmpA* and *peg-344*. Intravenous amoxicillin-clavulanic acid was administered based on the susceptibility test for 6 weeks, the abscess was drained and he was discharged well. *Discussion:* Hypervirulent *Klebsiella pneumoniae* are reported worldwide to cause liver abscess and extrahepatic metastasis. A recent study suggested five biomarkers; *peg-344, iroB, iucA, rmpA* and *rmpA2* that could accurately identify hvKp. As hvKP poses a thick capsule, it is less likely to harbour antimicrobial resistance. However, multidrug-resistant hvKp is emerging, likely due to integration of virulence genes into drug resistance plasmids via horizontal transfer. Therefore, contact precautions should strongly be considered and infection control team should be alerted for appropriate management of multidrug-resistant hvKp.

MM36: Unmasking a rare case of ESBL *Escherichia coli* meningitis in a patient after lumbar spine surgery

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Introduction: Postoperative bacterial meningitis is a rare complication of spinal surgery. A high index of suspicion for meningitis is essential in patients who have the clinical triad of fever, neck stiffness and severe headache. *Case report:* A 44 years old male complained of lower back pain with left lower limb radiculopathy symptoms for the past four months. Prolong sitting, sneezing, coughing, and straining aggravate the symptoms. Patient underwent open hemilaminectomy and partial discectomy. Intravenous ceftriaxone 2gm 12 hourly was administered as post-surgical prophylaxis. At day six post operation, the patient started to complain of headache, nausea, and vomiting associated with tachycardia, fever and desaturation that required oxygenation. Blood analysis showed high total white blood cell count, predominantly neutrophils. Analysis of CSF from the lumbar drain showed presence of pus cell and numerous gram-negative bacilli with elevated protein and low glucose. The pus swab, dura swab, superficial tissue, spinal process tissue and L3/L4 lamina bone were sent for culture and sensitivity (C&S) test, and was positive for ESBL *E.coli*. Intravenous meropenem 2gm 8 hourly was initiated based on cultures and sensitivity results. The patient clinically improved, cultures became negative after initiation of meropenem and patient discharges well after 2 weeks of meropenem. *Discussion:* ESBL *E.coli* meningitis is rare in adults, developing mainly as a complication of craniotomy, ventricular catheters, lumbar puncture, intrathecal infusions, or spinal anaesthesia and head injury. Most of the patients had either CSF leakage noted during the operation or from massive amounts of clear fluid drainage postoperatively.

MM37: A fatal disseminated penicilliosis in an unexplained CD4+ lymphopenia patient

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Introduction: Penicillium species has emerged as an opportunistic pathogen in immunocompromised hosts causing invasive fungal infections (IFIs) with high mortality. *Case report:* We reported a 29-year-old male presenting with prolonged fever and dyspnoea. A physical examination revealed lymphadenopathy, hepatomegaly and crepitations on the right lung. Further investigations showed bicytopenia and Computed Tomography revealed right lung collapsed consolidation with nodules and cavitation. Multiple courses of broad-spectrum antibiotics were initiated for sepsis but fever continues to persist. All microbiological cultures from various clinical specimens remained negative. Histopathological examination of supraclavicular lymph node and bone marrow trephine biopsy exhibited chronic granulomatous with fungal bodies. Direct panfungal PCR from the histology specimen targeting the ITS region followed by Sanger's sequencing confirmed as *Penicillum sp*ecies. TB and HIV screening were negative with inversely low CD4 counts. The patient succumbed to his illness despite on amphotericin

B and itraconazole. *Discussion:* This case illustrates the role of molecular testing is crucial to support the diagnosis of IFIs in situations where culture investigations were inconclusive. Antifungal susceptibility and resistant gene testing can guide clinicians to tailor appropriate antifungal treatment, but this is mostly applicable if the fungus is culturable. The immunocompromised state of this patient with CD4+ lymphopenia (HIV-negative) remained as a diagnostic dilemma but can also be attributable to severe systemic infection. *Conclusion:* Early recognition of IFIs require a complex diagnostic approach when the gold standard culture method is negative. Surgical removal of foci of infection together with Amphotericin B may be useful in most clinical situations.

MM38: Membranous nephropathy as the initial clinical presentation in a patient with newly diagnosed HIV and syphilis co-infection

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Introduction: Membranous nephropathy (MN) is a type of glomerular disease characterised by immune complexes deposition in the subepithelial region with thickening of glomerular basement membrane. In majority, the aetiology of the condition is unknown. *Case report:* A young male in early 30s presented with a ten days history of frothy urine associated with abdominal distension and bilateral lower limb oedema. His urinalysis revealed significant proteinuria of 5 g/L abnormal protein creatinine ratio at 1.53 g/mmol creatinine suggestive of nephrotic syndrome. Other abnormal laboratory results included hypoalbuminemia, hypercholesterolemia and elevated alkaline phosphatase. The renal biopsy was subsequently performed and demonstrated glomerular basement membrane thickening and subepithelial deposit which is in keeping with membranous nephropathy. The anti-nuclear antibody was positive at a very low titre. The screening for HIV and syphilis infections were also positive. Upon further questioning, the risk behaviour of MSM was revealed. Thus, MN was most likely due to HIV and syphilis co-infection. Intramuscular Benzathine penicillin 2.4 MU weekly for 3 weeks and daily tablet abacavir/lamivudine with tablet dolutegravir were initiated. He responded well to treatment with complete resolution of the symptoms and proteinuria at two- and six-weeks follow-up. *Discussion:* Although the underlying condition that leads to MN is unknown in majority of the cases, it is worth investigating for the possible secondary causes as the prognosis of secondary MN is based on the successful treatment of the underlying diseases. Both HIV and syphilis can contribute to MN but MN is a rare initial clinical presentation in both infections.

MM39: Immunomodulatory effects of nafamostat mesylate on dengue-infected sera induced endothelial cell dysfunction

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Introduction: Endothelial dysfunction, increased vascular permeability and plasma leakage are the underlying mechanisms in dengue haemorrhagic fever and dengue shock syndrome. Nafamostat mesylate (NM), a serine protease inhibitor, has demonstrated the ability to reverse vascular permeability in dengue-infected mouse model. This study aims to investigate the effects of NM in dengue-infected sera (DIS)-induced endothelial dysfunction through the expression of adhesion molecules in human umbilical vein endothelial cells (HUVEC). *Methods:* The effect of NM on viability of HUVEC was determined by MTT assay. Reactive oxygen species (ROS) production by DIS-induced HUVEC was determined by ROS study. The effect of NM on ICAM-1, VCAM-1 and E-selectin expressions in DIS-induced HUVEC was determined using flow cytometry. *Results:* High cell viability (>80%) was observed in HUVEC treated with different concentrations of NM ranging between 0 to 100 μg/mL. NM at concentration of 10 μg/mL has been selected for subsequent experiments in this study. Significant production of ROS was observed in HUVEC incubated with 20% dengue positive sera (p<0.05). Flow cytometry analysis had shown no significant difference on the expressions of ICAM-1, VCAM-1 and E-selectin in DIS-induced HUVEC with or without NM treatment. *Conclusion:* There were no cytotoxic effects observed on HUVEC treated with the tested NM working concentrations. 20% of dengue positive sera can induce cellular stress in HUVEC. NM treatment on DIS-stimulated HUVEC did not significantly affect the expressions of ICAM-1, VCAM-1 and E-selectin.

MM40: A case report of neck abscess complicated with panopthalmitis caused by hypervirulent *Klebsiella pneumoniae*

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Introduction: Hypervirulent *Klebsiella pneumoniae* (HvKP) has raised as a concerning global pathogen in recent years and often results in abscess formation. It is an invasive variant that differs from classic *Klebsiella pneumoniae* that has the ability to spread metastatically and capable of causing deep seated infections such as pyogenic liver abscess, pneumonia, meningitis and endophthalmitis. *Case report:* We present a rare case of a neck abscess complicated with panophthalmitis that lead to perforated cornea in a 56-year-old woman with underlying diabetes mellitus and end stage renal failure. She presented with

1 month history of neck abscess associated with right eye conjunctivitis. Incision and drainage of the abscess and right eye evisceration done in our hospital. All the cultures including pus, tissue and intravitreal fluid grew *Klebsiella pneumoniae* which is susceptible to cephalosporins, beta-lactam inhibitor combinations and fluoroquinolone. The string test was positive to guide us in early identification. Molecular identification demonstrates the HvKP genes which are iroD, rmpA and peg. The patient was treated with intravenous amoxicillin/clavulanic acid and ciprofloxacin. However, due to widespread infection of HvKP with overwhelming sepsis complicated by carbapenem-resistant *Enterobacterales* bacteraemia, the patient succumbed to death despite the surgical intervention and administration of susceptible antibiotics. *Discussion:* In this case report we emphasize the importance of early diagnosis with adequate intervention and appropriate antimicrobial duration and therapy of HvKP infection can determine the outcome of the patient.

MM41: Secondary and co-infections in hospitalised COVID-19 patients: A multicentre cross-sectional study in Malaysia

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Introduction: Bacterial and fungal secondary and co-infections are commonly identified with viral respiratory infections. This study was undertaken to determine the incidence and factors associated with bacterial and fungal infections in patients with COVID-19 as well as antibiotics prescription pattern within the first and second wave of the outbreak in Malaysia. *Materials & Methods:* Clinical records of 3532 COVID-19 patients admitted to hospitals in Malaysia between 4th February to 4th August 2020 were analysed. Co-morbidities, clinical features, investigations, treatment and complications were captured using REDCap database. Culture and sensitivity tests results were retrieved from WHONET database. Univariate and multivariate regression analyses were used to identify associated determinants. *Results:* A total of 161 types of bacterial and fungal infections were found in 81 patients, *i.e.*, 2.3%. The most common bacterial cultures were Gram-negative *i.e., Pseudomonas aeruginosa* (15.3%) and *Klebsiella pneumoniae* (13.9%). The most common fungal isolates were *Candida albicans* (41.2%). Amoxycillin/clavulanic acid, ceftriaxone, piperacillin/tazobactam, meropenem and azithromycin were the five most frequently prescribed antibiotics. *Discussion:* The latter four were classified under "Watch" category in the WHO AwaRe list. Our data showed that bacterial and fungal secondary and co-infections were frequently found in severely ill COVID-19 patients and associated with a higher mortality rate.

MM42: A fatal case of an invasive pneumococcal disease in a toddler: Presumptive PCV13 vaccine failure attributed to a resistant strain of serotype 19A

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Introduction: Malaysia introduced pneumococcal conjugate vaccination (PCV) as a national infant immunisation programme in 2020. However, PCV efficacy is variable depending on serotype coverage. Rarely, vaccine failures and breakthroughs occur, representing a challenge for disease control efforts. We report a fatal case of serotype 19A-IPD in a previously healthy and fully immunised 2-year-old toddler. *Case Report:* The toddler held a completed immunisation certification for PCV-13 vaccine. He had a fever and cough, and was started on azithromycin on day 5 of the illness. Nevertheless, his symptoms deteriorated, with altered mentation. He was rushed to the hospital on day 9 of his illness. Chest X-rays confirmed pneumonia, and he had elevated CRP and severe metabolic acidosis. A rapid diagnostic test for respiratory viruses was negative. Post-mortem cerebral spinal fluid, blood, and pericardial fluid isolated *Streptococcus pneumoniae*, which was later confirmed as serotype 19A. The bacteria were resistant to penicillin and ceftriaxone. *Conclusion*: Despite the significant benefits of conjugated pneumococcal vaccine, variable protection against different serotypes has been demonstrated, particularly serotype 19A, which has shown a propensity for vaccine evasion in children in the PCV13 era. Vaccine failure was observed more in immunocompromised children, contrary to our case. However, enzyme-linked immunosorbent assay and opsonophagocytic assay titres for each vaccine serotype were not available to ascertain whether the case was a vaccine failure or breakthrough. The case accentuates the need to evaluate the immune response in vaccinated children for a better understanding of the mechanisms involved in vaccine failures and breakthroughs.

MM43: Exposing the unusual potential of *Streptococcus pyogenes*: A primary pyomyositis of vastus muscle in an immunocompetent child

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Introduction: "Tropical pyomyositis" is defined as primary muscle abscess within the striated muscle that occurs in tropical countries with high temperatures and humidity. *Staphylococcus aureus* remain the most common organism involved, followed by others such as *Streptococcus* sp., *Pseudomonas* sp., and *Klebsiella* sp. This case report describes an unusual case of primary pyomyositis of the vastus muscle caused by *Streptococcus pyogenes* in a previously healthy 12-year-old

boy. *Case Report:* The patient presented with a one-week history of worsening right thigh pain and fever following a fall during a football game. The initial diagnosis was viral myositis. However, subsequent imaging revealed an avulsion fracture of the right lesser trochanter apophysis complicated with an infected haematoma. The patient was treated with intravenous amoxicillin-clavulanate. He underwent ultrasound-guided drainage of the haematoma in which *Streptococcus pyogenes* was isolated from the pus aspirate. The patient recovered fully after a two-week hospital stay and continued oral antibiotics for another four weeks. *Discussion:* This case highlights a rare presentation of primary pyomyositis located in the vastus medialis muscle since iliopsoas is the most vulnerable anatomical site. Also, this case underlines the infrequent presentation of *Streptococcus pyogenes* intramuscular abscess diagnosed using intramuscular pus culture. Tropical pyomyositis should be considered in the differential diagnosis of any patient presenting with muscle pain, fever, and/or leukocytosis.

MM46: Diphyllobothriasis: An incidental finding in systemic lupus erythematosus patient

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Introduction: Diphyllobothriasis, commonly caused by *Diphyllobothrium latum* is rarely reported locally and was first reported in Malaysia in 2002. Humans acquire the infection after consuming raw or inadequately cooked infected fish. This is the third case reported in Malaysia. *Case report:* A 31-year-old Bidayuh lady with systemic lupus erythematosus (SLE) and lupus nephritis presented with a three-day history of fever, abdominal pain and passing watery stools. Intravenous ceftriaxone and metronidazole were given as empirical therapy for intra-abdominal sepsis. Laboratory findings showed a normal white cell count of 9.42 x 10^3/uL and an elevated C-reactive protein of 422.5 nmol/L. Ultrasound abdomen showed normal findings. *Streptococcus dysgalactiae* was isolated from her blood culture taken during admission. Subsequently, *Corynebacterium striatum* was isolated from repeated blood cultures on day five and nine of admission. Her antibiotics were changed to intravenous vancomycin and ampicillin. However, the patient persistently had watery stools since admission. Stool culture showed no enteric pathogen isolated while stool ova and cyst demonstrated eggs of *Diphyllobothrium latum*. Unfortunately, her condition deteriorated before anti-parasitic agents could be initiated. She passed away due to septic shock and severe SLE flare with acute on chronic renal failure. *Discussion:* While human Diphyllobothriasis is often asymptomatic, some patients may experience gastrointestinal symptoms. The use of corticosteroids and immunosuppressants for SLE treatment may cause severe symptoms, as evidenced by persistent diarrhoea in this patient. Therefore, a comprehensive history and proper work-up should be performed in immunocompromised individuals with gastrointestinal symptoms to rule out parasite infections.

MM47: Case report of nontuberculous mycobacterial infection mimicking tuberculosis in HIV patient: A real brain teaser

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Introduction: Nontuberculous mycobacteria (NTM) infections are often diagnosed in patients with primary immunodeficiency disease or advanced human immunodeficiency virus (HIV). The commonest causative agent is *Mycobacterium avium* complex (MAC). An advanced HIV infection increases NTM & *Mycobacterium tuberculosis* (MTB) acquisition. The NTM infection can resemble tuberculosis and the risk of overlooking NTM is high since MTB would be the first concern in HIV-positive patients with symptoms of pulmonary mycobacterial disease. *Case report:* Here we described a case of disseminated NTM in a young patient with advanced HIV that was initially treated as tuberculosis before the molecular test result. The patient manifested symptoms similar to tuberculosis, such as chronic cough with constitutional symptoms, which could be misdiagnosed as tuberculosis. The initial blood and sputum MTB culture results were reported as *Mycobacterium avium* only after three months. This case highlighted the diagnostic uncertainty that can arise when AFB smears are persistently positive yet negative for the molecular test. *Discussion:* Slow-growing NTM infection diagnosis can be challenging due to the similar presentation and findings of screening methods used. Early detection and treatment of NTM could save lives, reduce antimicrobial resistance, and minimise unnecessary healthcare expenses. A good clinical history, a high index of suspicion, and advanced laboratory methods can minimise turnaround time and provide a correct and rapid diagnosis of NTM. Rapid molecular-based diagnosis of NTM should be performed to identify the causative organism up to the species level as accurate species differentiation is crucial for prompt evidence-based treatment and optimal patient outcomes.

MM48: *Edwardsiella tarda*: A rare human pathogen causing bacteraemia

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Introduction: Edwardsiella tarda is found primarily in aquatic habitats. Although it is uncommon, it has been known to infect humans and cause gastroenteritis and other extraintestinal illnesses. However, fatal cases have been observed in immunocompromised people. This case demonstrates how *E. tarda* bacteraemia was successfully treated in an elderly diabetic patient with underlying cholecystitis. *Case report:* We described an 86-year-old diabetic man who arrived at an emergency department complaining of stomach pain, yellow sclera discoloration, passing tea-coloured urine, and a fever for three days. On examination, the patient was febrile, had jaundice, and had generalised abdominal discomfort over the epigastric and right hypochondriac regions, with a positive murphy sign. Blood tests revealed leukocytosis, primarily neutrophils, a high C-reactive protein level, and raised liver enzymes and bilirubin levels, suggestive of obstructive jaundice. An ultrasound of the abdomen revealed a dilated gallbladder with sludge and numerous calculi. Sensitive strains of *E. tarda* were identified

by the Maldi-TOF from his blood culture. The patient was diagnosed with sepsis secondary to acute calculous cholecystitis and *E. tarda* bacteraemia. The patient responded well with intravenous metronidazole and cefoperazone. He was sent home with oral cefuroxime. *Discussion:* Human infection with *E. tarda* is extremely rare (0.02%). To the best of our knowledge, this is the first case of *E. tarda* bacteraemia reported in Malaysia. Maldi-TOF is a novel diagnostic tool with higher accuracy in pathogen identification than routine commercial biochemical panels. The accuracy and speed of Maldi-TOF allowed early initiation of appropriate antimicrobial therapy, which subsequently improved the patient's outcome.

MM49: *Shewanella algae*: A rare organism causing meningitis in newborn

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Introduction: Shewanella spp. is a Gram-negative, non-fermenting bacilli which may cause sepsis leading to meningitis secondary to a wound infection. *Case report:* We report a case of *Shewanella algae* bacteraemia associated with meningitis. A baby was born via spontaneous vertex delivery at home under non-sterile conditions with a birth weight of 1.65kg. Her mother was a teenager with no antenatal follow-up. Ballard score estimated a gestational age of 34 weeks. She was brought to the hospital on day 2 of life with a superficial laceration wound over the right upper lid, presumably sustained at birth. She was lethargic with a poor tone. Other systemic examinations were normal. Septic workout revealed leukopenia and raised inflammatory markers. Blood culture grew mucoid non-lactose fermenting colonies on MacConkey agar and oxidase positive which was identified as *Shewanella algae* by Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) with the score of 2.30. Antibiotic susceptibility testing showed that the organism was susceptible to ceftazidime, cefepime and gentamicin. Lumbar puncture was suggestive biochemically but sterile. She completed fourteen days of intravenous cefotaxime and c-penicillin. Subsequently, the patient improved clinically and achieved clearance of blood culture. *Discussion: Shewanella algae* infections are rare, nevertheless, an increasing number of cases are being reported related to warm climate and saline water. Mostly the infections are skin and soft tissue in origin. In the case above, the baby was delivered at home in a non-sterile condition and sustained a superficial laceration wound which could be the source of infection leading to bacteraemia and subsequently meningitis.

MM50: Anaphylaxis: omega 5 gliadin or oral mites? Filling up the puzzle

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Introduction: Omega 5 gliadin (O5G) and oral mite consumption are among the triggering factors of anaphylaxis in food allergies. We presented a case of recurring anaphylactic reaction immediately after consuming wheat products. *Case report:* A 29-year-old female with underlying well controlled bronchial asthma presented with anaphylaxis after consuming wheat containing product. The first two episodes of anaphylaxis (urticaria and dyspnoea) occurred after consuming fried noodles and 'roti canai' respectively. The third episode resulted in severe anaphylaxis (urticaria, angioedema, dyspnoea, and hypotension) requiring adrenaline and hydrocortisone which occurred after consuming donuts. No cofactors including exercise, NSAIDs consumption, alcohol, infection and menstruation were present. She had no food, drug, inhalant, and insect allergy previously. Total immunoglobulin E (IgE) and specific IgE were measured using the ImmunoCAP system (Thermo Scientific, Uppsala, Sweden). Total Ig E was elevated;1267 kU/L (normal:<100kU/L). Specific IgE were elevated to house dust mites; *Dermatophagoides pteronyssinus* (>100kuA/L; high), storage mites; *Lepidoglyphus destructor* (21.1kuA/L; high) and *Glyphagus domesticus* (11.9 kuA/L; moderate), wheat (0.85 kuA/L; low), and O5G (18.4 kuA/L; high). Microscopic examination of the wheat flour was not done to rule out oral mite anaphylaxis and no serum tryptase was sent. *Discussion:* This patient presented with adult-onset wheat induced anaphylaxis, where O5G served as an important marker, however, no cofactors were present. Apart from O5G allergy, oral mites could be considered a contributing factor to anaphylaxis. Awareness among the clinicians and further study on O5G and mites relation are important for accurate diagnosis and management of food allergies in the era of precision medicine.

MM51: Group B Streptococcus bacteraemia in adult patients at a tertiary care hospital in Malaysia – Incidence rates, clinical characteristics, mortality, and antibiotic susceptibility of isolates (2015-2019)

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Introduction: Group B Streptococcus (GBS) infection causes high mortality and morbidity in pregnant women, neonates, infants, the elderly, and adults; however, there have been limited local studies on adult GBS bacteraemia. *Materials & Methods:* A retrospective cohort study of adult patients with GBS bacteraemia at University of Malaya Medical Centre from January 2015 to December 2019. Bacteraemia was defined as at least 1 positive blood culture for GBS. *Results:* The incidence rate was 8.1 per 10,000 admissions (95% CI: 6.8, 9.4), with 95 (53.1%) females, 84 (46.9%) males, 28 (15.6%) maternal cases, and 74 (41.3%) aged ≥65 years. The majority (n = 125, 69.8%) of patients had community-acquired bacteraemia, while diabetes mellitus (n = 104, 58.1%), hypertension (n = 84, 46.9%), and chronic renal disease (n = 45, 25.1%) were the most common underlying illnesses. Among 43/179 (24%) adults without an underlying illness, 28 (65.1%) were pregnant or postpartum women. Polymicrobial bacteraemia occurred in 25 (14.0%) cases, with the most common microorganisms co-isolated with GBS being Staphylococcus aureus (n = 11), Coagulase-negative Staphylococcus (n = 7), and Klebsiella

pneumoniae (n = 4). Skin and soft tissue infections (n = 57, 31.8%) and primary bacteraemia (n = 41, 22.9%) were the two most common origins of GBS bacteraemia. The overall 14-day mortality rate was 15.7%, and shock at presentation increased the odds (OR = 42.95; 95% CI: 9.44,195.49) of mortality. All GBS isolates tested were susceptible to penicillin, ampicillin, and vancomycin. *Conclusion:* Larger prospective cohorts are needed to better understand the prognostic factors of GBS bacteraemia.

MM52: Carbapenem-resistant Enterobacterales: Risk factors, phenotypic identification, clinical features, and outcomes in a tertiary care hospital

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Introduction: Carbapenem-Resistant *Enterobacterales* (CRE) is the deadliest multidrug-resistant organism and a significant public health concern. This study aimed to identify carbapenemase-producing CRE isolates via phenotypic testing, Carbapenem Inactivation Method (CIM) and to determine risk factors and clinical outcomes among CRE patients. *Materials and Methods:* A prospective cross-sectional study of 58 CRE clinical isolates was conducted for one year. These CRE isolates were evaluated phenotypically for the detection of carbapenemases and their classification by modified EDTA-CIM. *Results: Klebsiella pneumoniae* was the most common isolated species accounting for 84.5%, and the majority were from critical care wards. Seventy-four per cent of CRE isolates produced carbapenemase and belonged to the Metallo-β-lactamase group. Two-thirds of CRE were caused by true CRE infection, with urinary tract infections being the most predominant CRE infection, 24.1%. Previous exposure to healthcare facilities ($p=0.04$), usage of antimicrobials of three classes and above, and patient comorbidities with $p<0.001$ and $p=0.03$ were identified as risk factors associated with CRE emergence. *Discussion:* Exposure to healthcare settings, multiple antibiotic usage, and comorbidities were the significant risk factors for CRE emergence. In conjunction with phenotypic testing, this may alert clinicians to the necessity of CRE screening and CRE phenotypic testing before critical care unit admission, thereby mitigating CRE spread. Effective antibiotic stewardship and infection prevention measures are vital.