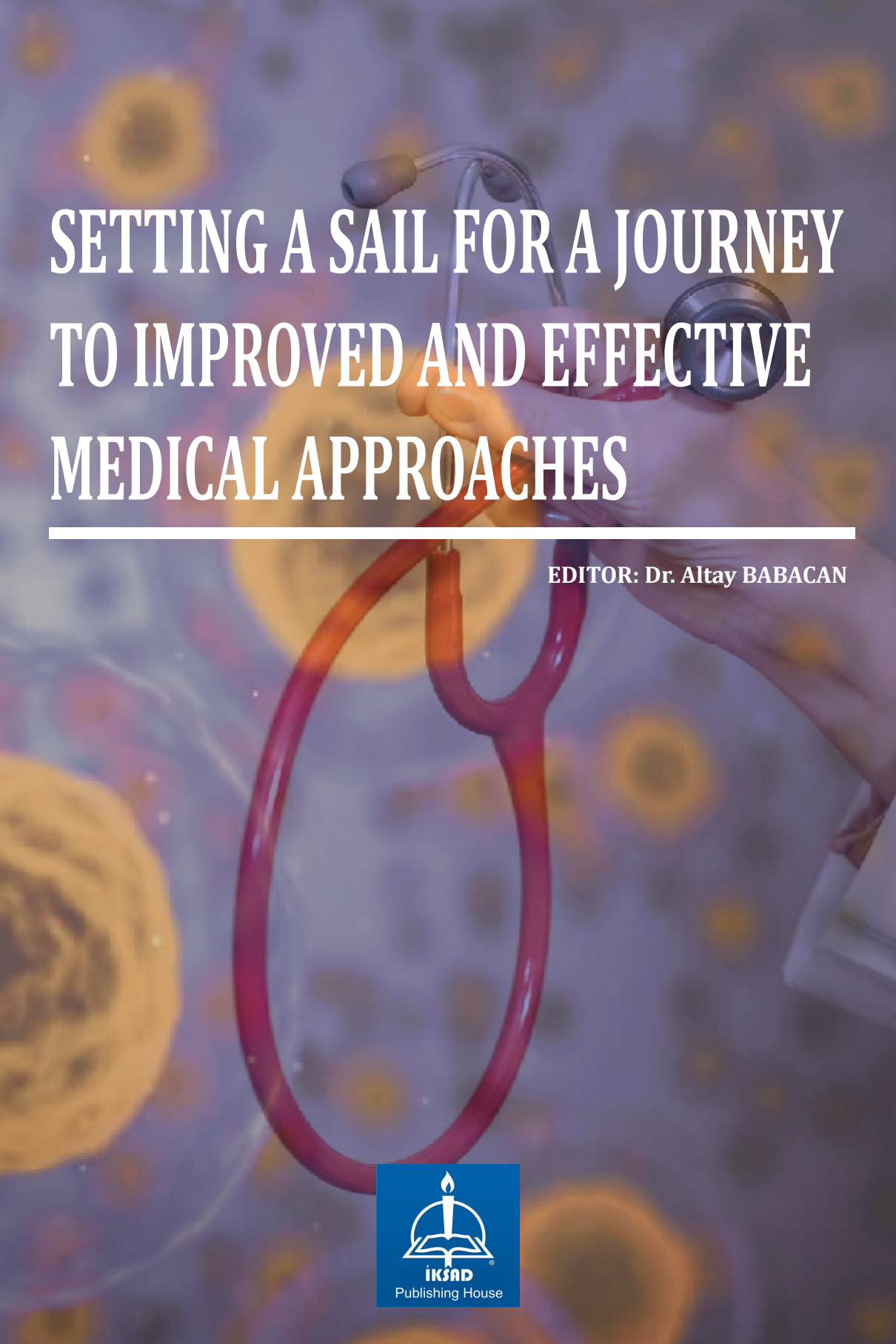

SETTING A SAIL FOR A JOURNEY TO IMPROVED AND EFFECTIVE MEDICAL APPROACHES

EDITOR: Dr. Altay BABACAN

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PREFACE

Many common agendas and quick guides are needed to built an integrated approach for early detection, screening, identification, classification, evaluation and treatment of diseases for the clinical usage of preventive services task forces supported with next generation nurses educated on genetics, genomics and risk assessments in the new decade. Updating guidelines for the management of inflammation and infection control, cancer prevention, cardiovascular diseases, diabetes and other major public health concerns have priority.

Holistical understand of the current perspectives on causal mechanisms, risk factors, complications, strategies, genetic susceptibility, responsibility of the individuals, reflection of childhood diseases in adulthood, chemistry and pharmacology of drugs, assessment and management of clinical problems is highly required. Also foods scientifically proven to prevent and reverse diseases, improving care and quality of life, diagnosis-related care, nursing care planning are important parts of sustainable long-term management of medical applications which should be considered.

These are some of subjects reader may find in this book which is supported with diversified fresh knowledge from quality researches.

Dr. Altay BABACAN

CHAPTER 1

PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS: A REVIEW

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1. Introduction

Central nervous system tumors are leading causes of morbidity and mortality in childhood. These are medulloblastoma, ependymoma, pilocytic astrocytoma, glioblastoma, diffuse intrinsic pontine glioma, atypical teratoid/rhabdoid tumors, and choroid plexus tumors. Medulloblastoma is a malignant childhood cerebellar tumour type comprising distinct molecular subgroups. Ependymomas are tumors which may arise in supratentorial brain, hindbrain or posterior fossa or anywhere in the spinal cord in children. Pilocytic astrocytomas, as a group, are relatively benign and have 10-year survival of <90%. Pediatric glioblastoma is among the most common malignant brain tumors of childhood.

Here in this review, reader may find some cureent infos related to pediatric central nervous system tumors.

Aggressive central nervous system tumors are leading causes of morbidity and mortality in childhood. Pediatric central nervous system tumors are medulloblastoma, ependymoma, pilocytic astrocytoma, glioblastoma, diffuse intrinsic pontine glioma, atypical teratoid/rhabdoid tumors, and choroid plexus tumors (Pezuk et al., 2019). Exposure to certain pesticides of residential proximity to agricultural field applications of pregnant women may increase risks of childhood central nervous system tumors (Lombardi et al., 2021). Survivors of childhood central nervous system tumors experience elevated rates of treatment-related neurologic sequelae. Cranial radiation, tumor recurrence, stroke, and development of meningioma

were independently associated with late-onset adverse neurologic sequelae by Wells et al., (2018).

2. Medulloblastoma

Medulloblastoma is a malignant childhood cerebellar tumour type comprising distinct molecular subgroups. Genomic characteristics of subgroups are well defined, but their cellular diversity underling their divergent biology and clinical behaviour is mostly unexplored (Hovestadt et al., 2019). The molecular characterisation of this heterogenous disease is required for true management and treatment. But insufficient tissue sample, presence of tumour heterogeneity, or disseminated disease is challenging its diagnosis and monitoring (Escudero et al., 2020). Medulloblastoma is the most common type of brain malignancy in children. Molecular profiling is important to select patients for therapeutic approaches to allow personalized therapy. Cerebrospinal fluid supernatant can be used to monitor genomic alterations, as a superior technique as long as tumor-derived cfDNA (cell-free nucleic acids including DNA) can be isolated from cerebrospinal fluid successfully (Sun et al., 2021).

Alteration of chromatin is deregulated in many cancers. Medulloblastoma is an embryonal tumor of the cerebellum which occurs rarely in adults. Medulloblastoma is characterized by four major molecularly and histopathologically distinct groups: 1) wingless (Wnt), 2) sonic hedgehog (Shh), 3) “group 3”, 4) “group 4”. Except Wnt, each now subdivided in several subgroups. Medulloblastomas harbor a paucity of mutations most of which occur in epigenetic regulators,

genetic alterations in oncogenes and tumor suppressors, in addition to copy number alterations and chromosome gains and losses. Some tumors does not have reported mutations, suggesting that some genes required for oncogenesis might be regulated by epigenetic mechanisms (Roussel & Stripay, 2018).

3. Ependymoma

Ependymomas are tumors of the central nervous system. They may arise in supratentorial brain, hindbrain or posterior fossa or anywhere in the spinal cord in children and adults. Molecular profiling studies were identified distinct groups and subtypes in each given anatomical compartments (Jenseit et al., 2021). Ependymoma is the 3rd most common brain tumor in children. Current treatment is not sufficient to provide long-term cure for children (Marinoff et al., 2017). Molecularly and a histologically, spinal ependymal tumors form heterogeneous group of tumors with generally good prognosis. But their treatment may be challenging if infiltration of the spinal cord or dissemination throughout the central nervous system occurs. For these cases, clinical outcome remains poor (Ghasemi et al., 2019). Proton therapy is a safe and efficacious for the re-treatment of recurrent pediatric intracranial ependymoma (Eaton et al., 2015).

4. Pilocytic astrocytoma

Pilocytic astrocytoma is the most common primary brain neoplasm in children and treated in curative intent with gross total resection. It is rare in adults, resulting in limited knowledge on the natural clinical course. Higher age and body mass index are associated with impaired

prognosis (Mair et al., 2020). Pilocytic astrocytoma survival was found to be worse among infants (Tabash, 2019). Pilocytic astrocytomas, as a group, are relatively benign (WHO grade I) and have 10-year survival of <90%. Many require merely surgical removal and only very infrequently do they progress to more malignant gliomas. While most show classical morphology, they may present a spectrum of morphological patterns, and there are difficult cases that show similarities to other gliomas, some of which are malignant and require aggressive treatment. The use of high-throughput sequencing techniques interrogating the whole genome revealed that single abnormalities of the mitogen-activating protein kinase pathway are exclusively found in almost all cases, indicating that pilocytic astrocytoma represents a one-pathway disease (Collins et al., 2015).

Rare cases of pilocytic astrocytoma present with anaplastic features, including an unexpected high mitotic/proliferative index, which pose a diagnostic and therapeutic challenge. Based on small histomolecular series and case reports, such tumors arising at the time of diagnosis or recurrence have been designated by many names including pilocytic astrocytoma with anaplastic features. Recent DNA methylation-profiling studies performed mainly on adult cases have revealed that pilocytic astrocytoma with anaplastic features exhibit a specific methylation signature, and constituting a distinct methylation class from typical pilocytic astrocytoma (methylation class anaplastic astrocytoma with piloid features). But diagnostic and prognostic significance of “methylation class anaplastic astrocytoma with piloid feature” remains to be determined in children (Gareton et al., 2020).

In the majority of pilocytic astrocytomas cases tumors are benign and receive favorable prognosis following gross total surgical resection. In patients with progressive or symptomatic tumors, aggressive surgical resection is frequently not feasible, thus radiation or chemotherapy are accepted initial or adjuvant interventions. Due to serious long-lasting side-effects, radiation is limited in young children. So, chemotherapy is widely practiced as an adjuvant treatment for these patients. However, chemotherapy can promote the emergence of multidrug resistant tumor cells that are more malignant than those of the original tumor. Cell surface marker CD133 (also known as AC133 and prominin-1 which are used as cell surface antigen to detect and isolate cancer stem cells from various solid tumors including brain, colon, pancreas, prostate, lung, and liver), is a putative stem cell marker in normal tissue and malignant brain tumors and enhances "multidrug resistant gene 1" expression following chemotherapy in adult malignant glioblastomas (Xi et al., 2017).

5. Glioblastoma

Pediatric glioblastoma is among the most common malignant brain tumors of childhood and carries a dismal prognosis. In contrast to adult glioblastoma, few molecular prognostic markers for the pediatric counterpart was established (Korshunov et al., 2015). Pediatric glioblastoma is an extremely aggressive pediatric brain tumor, accounting for ~6% of all central nervous system neoplasms in children. Approximately 1/2 of pediatric glioblastoma harbor recurrent somatic mutations in histone 3 variants or, infrequently, "Isocitrate

dehydrogenase 1" and "Isocitrate dehydrogenase 2". The remaining subset of pediatric glioblastoma is highly heterogeneous, and displays a variety of genomic and epigenetic features (Korshunov et al., 2017).

Gross total resection is essential for longer overall survival among pediatric patients with glioblastoma and offers a possibility for long-term survival. Severity of neurologic symptoms quantified by neurologic function score can be considered as a potential predictor of outcome (Nikitovic et al., 2016). Gross total resection is independently associated with improved survival for pediatric patients with glioblastoma (Adams et al., 2016).

While the 5-year overall survival is better in pediatric than in adult patients diagnosed with glioblastoma, outcomes in children remain very poor. In situ hybridization positive samples show high concordance with being pp65 or IE1-72 (human cytomegalovirus proteins) positive. Paired with the association of human cytomegalovirus expression with poor prognosis and overall survival, indicate the need to further investigate how these antigens are promoting tumor growth and preventing cell death. Also, the expression of these antigens in a majority of tumor tissues should be considered for immunotherapeutic targets in cases of pediatric glioblastoma (Wakefield et al., 2015).

6. Diffuse intrinsic pontine glioma

Pediatric diffuse intrinsic pontine glioma represents approximately 20% of all pediatric central nervous system tumors. However, disease outcomes are dismal with a median survival of less than one year and a two-year overall survival rate of less than 10%. To improve survival

outcomes, progress for clinical improvement was largely stagnant throughout the last four decades. Focal radiotherapy remains the standard of care with no promising single-agent alternatives and no evidence for improvement with the addition of a long list of systemic therapies. A better understanding of the biology of diffuse intrinsic pontine glioma, though not easy due to obstacles in obtaining pathological material to study, is promising for the development of specific individualized treatment for this fatal disease. Recent studies have found epigenetic mutations to be successful predictors and prognostic factors for developing future management policies (Rashed et al., 2019).

Citrate, a tricarboxylic acid cycle intermediate, is present in high concentrations in pediatric diffuse intrinsic pontine gliomas. Citrate accumulation is associated with tissue hypoperfusion in diffuse intrinsic pontine gliomas (Yeom et al., 2015). There is a paucity of data regarding patterns of progression in children with high-grade glioma or diffuse intrinsic pontine glioma treated with bevacizumab at diagnosis. Bevacizumab may lead to a higher incidence of distant and diffuse disease in newly-diagnosed children with high-grade glioma or diffuse intrinsic pontine gliomas who received bevacizumab-based therapy (Salloum et al., 2015).

Baseline diffusion or apparent diffusion coefficient characteristics were shown to predict outcome related to diffuse intrinsic pontine glioma, but the predictive value of post-radiation apparent diffusion coefficient is not well understood. Baseline apparent diffusion coefficient values

are a stronger predictor of outcome compared to radiation related apparent diffusion coefficient changes in pediatric diffuse intrinsic pontine glioma. Feasibility of employing parametric mapping techniques in multi-center studies to quantitate spatially heterogeneous treatment response in pediatric tumors, including diffuse intrinsic pontine glioma was show by Ceschin et al., (2019).

7. Atypical teratoid/rhabdoid tumors

Cancer is often seen as a disease of mutations and chromosomal abnormalities. However, some cancers, including pediatric rhabdoid tumors, lack recurrent alterations targetable by current drugs and need alternative therapeutic options. Perturbational screens may identify vulnerabilities not detectable in genomic analyses. Large-scale perturbational screening can uncover vulnerabilities in cancers with "quiet" genomes. Receptor tyrosine kinases inhibitors are effective against a xenografted rhabdoid mouse model in vivo (Oberlick et al., 2019). Pediatric non-central nervous system malignant rhabdoid tumors are rare and aggressive malignancies without standard treatment strategies. Patients with non-central nervous system malignant rhabdoid tumors who were diagnosed in infancy and had metastatic disease had worse survival outcomes. Although surgical resection was associated with improved survival in non-central nervous system malignant rhabdoid tumors, it was not independently associated with survival on multivariate analysis. Efforts to improve survival may instead depend on improving chemotherapeutic strategies and developing targeted therapies (Morgan et al., 2022).

The optimal treatment strategy for pediatric atypical teratoid rhabdoid tumor is inconclusive. Both early radiotherapy initiation and high-dose chemotherapy with autologous stem cell rescue were important components in the treatment of pediatric atypical teratoid rhabdoid tumor. However, the optimal treatment strategies might differ by age (Yang et al., 2020).

Although pediatric atypical teratoid rhabdoid tumors patients are a highly vulnerable group, maximal resection is recommended where possible, for the best chance of long-term survival. However, near total resections are likely beneficial when compared with subtotal resections and biopsy alone. Maximal surgical resection should be combined with adjuvant therapies for the best long-term outcomes (Richards et al., 2020). Central nervous system atypical teratoid rhabdoid tumor have poor outcomes. Despite known leptomeningeal spread no consensus exists regarding focal or craniospinal radiation, typically given after surgery and chemotherapy. Practice patterns strongly favored focal radiation therapy and 54Gy showed improved local control. Further radiation field in atypical teratoid rhabdoid tumor will be challenging due to prohibitive toxicity of craniospinal radiation in infant brain tumors (Roehrig et al., 2021).

8. Choroid plexus tumors

Protein misfolding and aggregation result in proteotoxic stress and underlie the pathogenesis of many diseases. To overcome proteotoxicity, cells compartmentalize misfolded and aggregated proteins in different inclusion bodies. The aggresome is a paranuclear

inclusion body that functions as a storage compartment for misfolded proteins. Choroid plexus tumors are rare neoplasms comprised of three pathological subgroups. Results support the role of aggresome as a novel prognostic molecular marker for pediatric choroid plexus tumors that was comparable to the molecular classification in segregating samples into two distinct subgroups, and to the pathological stratification in the prediction of patients' outcomes. Moreover, the proteogenomic signature of choroid plexus tumors displayed altered protein homeostasis, manifested by enrichment in processes related to protein quality control (Amer et al., 2021). Choroid plexus tumors are rare neoplasms accounting for 1–4% of all pediatric brain tumors. They are divided into choroid plexus papilloma, atypical choroid plexus papilloma and choroid plexus carcinoma. Choroid plexus tumors are known to primarily affect children less than two years of age. Gross total resection is the major predictor of survival especially in choroid plexus carcinoma (Bahar et al., 2017). Dudley et al., (2015) analysed "The National Cancer Institute"s "Surveillance, Epidemiology and End Results" Program which is a well-established population-based group of collects and publishes on cancer incidence and survival data representing approximately 28% of the US population. The "Surveillance, Epidemiology and End Results" registries contained 107 choroid plexus papillomas (2004–2010) and 95 choroid plexus carcinomas (1978–2010). Median follow-up was 38 and 40 months, respectively. <75% of choroid plexus carcinomas were diagnosed before the age of five years, versus 48% for choroid plexus papillomas. 65% of choroid plexus carcinomas and 57% of choroid plexus

papillomas occurred in males. In both groups <90% of children underwent surgical resection. Gross total resection was achieved in 67% of choroid plexus carcinomas and 64% of choroid plexus papillomas. Almost 17% of choroid plexus carcinomas were treated with radiation versus only 1% of choroid plexus papillomas. More than 98% of patients with choroid plexus papilloma were alive at the last follow-up, versus 62% of choroid plexus carcinoma patients. For choroid plexus carcinoma, surgery was significantly associated with increased overall survival, but contrary to previous reports, extent of surgical resection was not associated with survival. Age, sex, race, and radiation treatment also had no effect on survival. As a result, they concluded that choroid plexus carcinoma occurs in younger children, with a male predominance, and a much worse prognosis than choroid plexus papilloma. These tumors were treated aggressively with high rates of gross total resection and radiation treatment. Despite these treatments, overall survival for choroid plexus carcinoma remains poor (Dudley et al., 2015).

9. Conclusions

For medulloblastoma, cerebrospinal fluid supernatant can be used to monitor genomic alterations, as a superior technique as long as tumor-derived cfDNA (cell-free nucleic acids including DNA) can be isolated from cerebrospinal fluid successfully. Proton therapy is a safe and efficacious for the re-treatment of recurrent pediatric intracranial ependymoma. For pilocytic astrocytomas in young children, chemotherapy is widely practiced as an adjuvant treatment but,

chemotherapy can promote the emergence of multidrug resistant tumor cells that are more malignant than those of the original tumor. Approximately 1/2 of pediatric glioblastoma harbor recurrent somatic mutations in histone 3 variants or, infrequently, “Isocitrate dehydrogenase 1” and “Isocitrate dehydrogenase 2”. Citrate accumulation is associated with tissue hypoperfusion in diffuse intrinsic pontine gliomas. Both early radiotherapy initiation and high-dose chemotherapy with autologous stem cell rescue were important components in the treatment of pediatric atypical teratoid rhabdoid tumor. Gross total resection is the major predictor of survival especially in choroid plexus carcinoma.

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CHAPTER 2

INHERITED AND ACQUIRED BONE MARROW FAILURES AND CURRENT TREATMENTS

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1. Inherited bone marrow failures

Here in this review, the genetic causes, clinical features, diagnostic modalities, predisposition to malignancies and approaches to treatments of the classical inherited marrow failure syndromes named 1) “Fanconi anemia”, 2) “Dyskeratosis congenita”, 3) “Shwachman Diamond syndrome”, 4) “Diamond blackfan anemia” and 5) “Severe congenital neutropenia” were short reviewed firstly. Followingly, acquired bone marrow syndromes named 1) acquired aplastic anemia, 2) myelodysplastic syndromes, 3) paroxysmal nocturnal hemoglobinuria, and 4) acquired amegakaryocytic thrombocytopenia was the subject.

The inherited marrow failure syndromes are a heterogeneous group of diseases characterized by failure in the production of one or more blood lineage. The clinical manifestations of the inherited marrow failure syndromes vary according to the type and number of blood cell lines involved, including different combinations of anemia, leukopenia, and thrombocytopenia. In some inherited marrow failure syndromes, systemic non-hematologic manifestations, including congenital malformations, mucocutaneous abnormalities, developmental delay, and other medical complications, may be present (Savage & Dufour, 2017).

Precise genetic diagnosis of inherited bone marrow failure syndromes, a heterogeneous group of genetic disorders, is challenging but essential for precise clinical decision making. Utilizing targeted sequencing and whole-exome sequencing achieved satisfactory diagnostic rates and supported the efficacy of massive parallel sequencing as a diagnostic

tool for Inherited bone marrow failure syndromes (Muramatsu et al., 2017).

Inherited bone marrow failure are diseases with hematopoietic failure and a wide array of physical malformations. Copy number variants were reported in some inherited bone marrow failure syndromes. It is unclear what impact copy number variants play in patients evaluated for a suspected diagnosis of inherited bone marrow failure syndromes. a significant proportion of patients with inherited bone marrow failure syndromes harbor pathogenic copy number variants which were associated with a more extensive non-hematological phenotype (Waespe et al., 2017).

Inherited bone marrow failure syndromes are disorders with cytopenia and many also with physical malformations and increased risk of cancer. Point mutations can be identified in about half of patients. Copy number variation copy number variations have been reported. However, the frequency and spectrum of copy number variations are unknown. Unfortunately, current genome-wide methods have major limitations since they may miss small copy number variations or may have low sensitivity due to low read depths. Careful analysis of normalized coverage values can detect copy number variations should be considered as a standard practice prior to do further investigations (Lauhasurayotin et al., 2019).

1.1. Fanconi anemia

Fanconi anemia, caused by germline pathogenic variants in the DNA repair genes comprising the FA/BRCA (Fanconi Anemia/Breast Cancer

genes) pathway is associated with congenital anomalies, bone marrow failure, and increased risk of myelodysplastic syndrome, acute myelogenous leukemia, and solid tumors (Savage & Dufour, 2017).

Fanconi anemia should be considered in adults of any age with a family history of aplastic anemia, acute myelogenous leukemia or myelodysplasia, or squamous cell carcinoma at an unusually young age. This disease can be ruled out by obtaining a chromosomal breakage test. There are at least 22 different fanconi anemia genes, and identification of the particular mutated gene using modern DNA sequencing methods is now widely utilized and important for prognostic information and for family screening and planning purposes. Fanconi genes (FANCA, FANCC, and FANCG genes) mutations account for the majority of cases so initial sequencing can focus on these. Knowing the particular gene involved is essential if preimplantation genetic diagnosis and in vitro fertilization is planned, an approach that has successfully resulted in unaffected offspring and ideal cord blood stem cell donors for transplantation of an affected sibling. Novel mutations can be distinguished from inconsequential sequence variants using gene complementation analysis in which the mutant gene is introduced into a cell line of an established fanconi anemia patient with a known mutation of the suspect gene (Bagby, 2011).

Fanconi anemia is a recessively inherited disorder associated with progressive bone marrow failure (aplastic anemia), and a high incidence of malignancies, which cause a strongly reduced life expectancy. The anemia can be cured by transplantation of bone marrow stem cells from

a compatible donor. Cells derived from patients with fanconi anemia are hypersensitive to agents that cause cross-links in the DNA. This feature is used to confirm a diagnosis of fanconi anemia. Currently, there are a series of distinct genes that cause fanconi anemia when mutated. The proteins encoded by these genes function in a biochemical pathway named fanconi anemia pathway to maintain the integrity of the genetic information during the process of DNA replication (de Winter & Joenje, 2013).

Fanconi anemia is the most frequent inherited cause of bone marrow failure. Most fanconi anemia patients experience hematopoietic stem cell attrition and cytopenia during childhood. Allogeneic hematopoietic stem cell transplantation is the only curative treatment for fanconi anemia patients in case of bone marrow failure or clonal evolution such as acute myeloid leukemia or myelodysplastic syndrome. Human leukocyte antigen identical hematopoietic stem cell transplantation is the best treatment. Alternative transplantation such as cord blood-, mismatch-, or haplo-hematopoietic stem cell transplantation are experimental (Aljurf et al., 2016).

Fanconi anemia is a rare autosomal and X-linked genetic disease with median lifespan approximately 33 years for patients. The proteins encoded by the fanconi anemia genes function together in the FA-BRCA pathway to repair DNA damage and to maintain genome stability. Within the past two years, five new fanconi anemia genes have been identified (RAD51/FANCR, BRCA1/FANCS, UBE2T/FANCT,

XRCC2/FANCU, and REV7/FANCV) bringing the disease-causing genes number to total 21 (Mamrak et al., 2017).

Fanconi anemia is characterized by progressive bone marrow failure from hematopoietic stem and progenitor cell attrition. Inhibition of signaling in fanconi anemia hematopoietic stem and progenitor cells results in elevated homologous recombination repair with a concomitant decrease in non-homologous end-joining, accounting for the improvement in cellular growth. Elevated transforming growth factor-β signaling contributes to bone marrow failure in fanconi anemia by impairing hematopoietic stem and progenitor cell function and may be a potential therapeutic target for the treatment of fanconi anemia (Zhang et al., 2016).

1.2. Dyskeratosis congenita

Dyskeratosis congenita is a telomere biology disorder caused by aberrations in key telomere biology genes. In addition to mucocutaneous manifestations, patients with dyskeratosis congenita are at increased risk of marrow failure, myelodysplastic syndrome, acute myelogenous leukemia, pulmonary fibrosis, and other complications (Savage & Dufour, 2017).

Dyskeratosis congenita is a complex syndrome exhibiting marked clinical and genetic heterogeneity. Classic dyskeratosis congenita form is characterized by mucocutaneous abnormalities, bone marrow failure, and a predisposition to cancer. Studies over years led to significant advances resulted with characterized 10 dyskeratosis congenita genes (DKC1, TERT, TERC, NHP2, NOP10, TINF2, C16orf57/USB1,

CTC1, TCAB1, and RTEL1). Nine of these are important in telomere maintenance, and patients usually have very short telomeres. These genetic advances have led to the unification of dyskeratosis congenita with a few other severe disorders such as Hoyeraal-Hreidarsson and Revesz syndromes, which are frequently characterized by a variable immune deficiency. This wide spectrum of diseases ranging from classic dyskeratosis congenita to Hoyeraal-Hreidarsson can be regarded as disorders of defective telomere maintenance – "the telomereopathies" (Dokal, 2014)

1.3. Diamond Blackfan anemia

Diamond Blackfan Anemia is a congenital bone marrow failure syndrome associated with ribosomal gene mutations that lead to ribosomal insufficiency. Diamond Blackfan Anemia is characterized by anemia, congenital anomalies, and cancer predisposition. Treatment for Diamond Blackfan Anemia is associated with significant morbidity (Wilkes et al., 2020).

Ribosomal biology defects are the primary causes of Diamond Blackfan anemia and Shwachman Diamond syndrome. In addition to pure red blood cell aplasia, Diamond Blackfan anemia is associated with elevated risk of solid tumors, acute myelogenous leukemia, and myelodysplastic syndrome (Savage & Dufour, 2017).

Identification of Nemo-like kinase is a potential target for Diamond Blackfan Anemia therapy. Chemical and genetic inhibition of Nemo-like kinase increases erythroid expansion in mouse and human

progenitors, including bone marrow cells from Diamond Blackfan Anemia patients (Wilkes et al., 2020).

Therapy of children with Diamond–Blackfan anemia has not advanced for decades. Corticosteroids, red blood cell transfusions and hematopoietic cell transplants are the only currently effective therapies. Each is associated with significant morbidity and mortality (Sakamoto & Narla, 2018).

Diamond-Blackfan anemia (DBA) was the first ribosomopathy described and is a constitutional inherited bone marrow failure syndrome. Erythroblastopenia is the major characteristic of the disease. This is a model for ribosomal diseases and related to a heterozygous allelic variation in 1 of the 20 ribosomal protein genes of either the small or large ribosomal subunit. The salient feature of classical Diamond-Blackfan anemia is a defect in ribosomal RNA maturation that generates nucleolar stress, leading to stabilization of p53 and activation of its targets, resulting in cell-cycle arrest and apoptosis. But activation of p53 may not explain all aspects of Diamond-Blackfan anemia erythroid tropism. Involvement of GATA1/HSP70 and globin/heme imbalance, with an excess of the toxic free heme leading to reactive oxygen species production, account for defective erythropoiesis in Diamond-Blackfan anemia. Progress in developing new therapeutic options is limited. However, advances in gene therapy, better outcomes with stem cell transplantation, and discoveries of new drugs are expected (Da Costa et al., 2020).

Diamond-Blackfan anemia is characterized by a profound normochromic and usually macrocytic anemia with normal leukocytes and platelets, congenital malformations in up to 50%, and growth deficiency in 30% of affected individuals. The hematologic complications occur in 90% of affected individuals during the first year of life. The phenotypic spectrum ranges from a mild form to severe form of fetal anemia resulting in nonimmune hydrops fetalis. Diamond-Blackfan anemia is associated with an increased risk for acute myelogenous leukemia, myelodysplastic syndrome, and solid tumors including osteogenic sarcoma. The clinical diagnosis can be established in a proband with macrocytic anemia with onset prior to age one year, no other significant cytopenias, reticulocytopenia, normal marrow cellularity with a paucity of erythroid precursors, and no evidence of another acquired or inherited disorder of bone marrow function. The molecular diagnosis can be established in a female proband by identification of a heterozygous pathogenic variant in one of the 22 genes associated with Diamond-Blackfan anemia. The molecular diagnosis can be established in a male proband by identification of a heterozygous pathogenic variant in a gene associated with autosomal dominant Diamond-Blackfan anemia or identification of a hemizygous pathogenic variant in GATA1 or TSR2 (Lipton & Alter, 2019).

For Diamond-Blackfan anemia treatment Corticosteroid is recommended in children older than age 12 months which improves the red blood cell count in approximately 80% of affected individuals. Chronic transfusion with packed red blood cells is necessary during the first year of life to avoid steroid-induced toxicity in those not responsive

to a trial of corticosteroids at age 12 months and in individuals who relapse. Hematopoietic stem cell transplantation, the only curative therapy for the hematologic manifestations of Diamond-Blackfan anemia, is often recommended for those who are transfusion dependent or develop other cytopenias. Treatment of malignancies should be coordinated by an oncologist. Chemotherapy must be given cautiously as it may lead to prolonged cytopenia and subsequent toxicities (Lipton & Alter, 2019).

1.4. Shwachman diamond syndrome

Inherited ribosomopathy Shwachman-Diamond syndrome is a bone marrow failure disorder with high risk of myeloid malignancies at an early age (Kennedy et al., 2021). Patients with Shwachman Diamond syndrome have pancreatic insufficiency, neutropenia, as well as myelodysplastic syndrome and acute myelogenous leukemia risks (Savage & Dufour, 2017).

Isomorphic mutation of the SBDS gene causes Shwachman-Diamond syndrome. Shwachman-Diamond syndrome is a rare genetic bone marrow failure and cancer predisposition syndrome. Shwachman-Diamond syndrome cells have ribosome biogenesis and their protein synthesis altered, which are two high-energy consuming cellular processes. The reported changes in reactive oxygen species production, endoplasmic reticulum stress response and reduced mitochondrial functionality suggest an energy production defect in Shwachman-Diamond syndrome cells (Ravera et al., 2016).

Shwachman-Diamond syndrome is an inherited disease caused by mutations of a gene encoding for Shwachman-Bodian-Diamond syndrome protein. So far little is known about Shwachman-Bodian-Diamond syndrome protein exact function. Shwachman-Diamond syndrome patients present several hematological disorders, including neutropenia and myelodysplastic syndrome, with increased risk of leukemic evolution. So far, the molecular mechanisms that underlie neutropenia, myelodysplastic syndrome and acute myeloid leukemia in Shwachman-Diamond syndrome patients have been poorly investigated. STAT3 is a key regulator of several cellular processes including survival, differentiation and malignant transformation. Moreover, STAT3 has been reported to regulate neutrophil granulogenesis and to induce several kinds of leukemia and lymphoma. STAT3 activation is known to be regulated by mammalian target of rapamycin, which in turn plays an important role in cellular growth and tumorigenesis (Bezzerri et al., 2016).

Allogeneic hematopoietic stem cell transplantation is a curative procedure in patients with Shwachman–Diamond syndrome with bone marrow abnormalities. Further efforts are needed to lower transplant-related toxicity and reduce graft failure (Cesaro et al., 2020).

1.5. Severe congenital neutropenia

Severe congenital neutropenia is a monogenic disorder. Severe congenital neutropenia patients are prone to recurrent life-threatening infections. The main causes of severe congenital neutropenia are autosomal dominant mutations in the ELANE (elastase neutrophil

expressed) gene that lead to a block in neutrophil differentiation (Tran et al., 2020).

Patients with severe congenital neutropenia, caused by pathogenic variants in genes essential in myeloid development, have profound neutropenia and high risk of myelodysplastic syndrome and acute myelogenous leukemia (Savage & Dufour, 2017).

Granulocyte colony-stimulating factor is a hematopoietic cytokine which stimulates neutrophil production and hematopoietic stem cell mobilization by initiating the dimerization of homodimeric granulocyte colony-stimulating factor receptor. Different mutations of CSF3R (colony stimulating factor 3 receptor) are linked to unique myeloid disorders and malignancies. Myeloid disorders caused by the CSF3R mutations include severe congenital neutropenia, chronic neutrophilic leukemia, and atypical chronic myeloid leukemia (Dwivedi & Greis, 2017).

Severe congenital neutropenia is described by the absolute neutrophil counts less than 500 cells/mm^3, bacterial infections, and arrest of neutrophil differentiation. Due to this, effective strategies to improve the function and lifespan of the existing neutrophils of these patients are necessary. Mesenchymal stem cells have supportive effects on neutrophils. It was recently determined that mesenchymal stem cells exert their effects, mostly by secreting soluble factors and exosomes (Mahmoudi et al., 2019).

2. Acquired bone marrow failures

Acquired bone marrow failure syndromes are heterogeneous diseases characterized by cytopenias caused by a decrease in or malfunction of hematopoietic stem/progenitor cells (HSPCs). These syndromes include 1) acquired aplastic anemia, 2) myelodysplastic syndromes, 3) paroxysmal nocturnal hemoglobinuria, and 4) acquired amegakaryocytic thrombocytopenia. Differential diagnosis is difficult as these syndromes are primarily defined by cell morphology. Hemolytic paroxysmal nocturnal hemoglobinuria is easily distinguishable from other forms. Patients with paroxysmal nocturnal hemoglobinuria present with unique symptoms and laboratory findings (hemoglobinuria and marked increase in serum Lactate dehydrogenase levels).

2.1. Acquired aplastic anemia

Aplastic anemia is characterized by pancytopenia and hypoproliferative reticulocyte count in the presence of a hypocellular bone marrow. If untreated, patients usually die from bleeding or infection. Although drugs (indomethacin, chloramphenicol, carbamazepine, methimazole, chloroquine), environmental toxins (benzene), viruses, and ionizing radiation were reported as causally associated with acquired aplastic anemia, the current understanding of the disease mechanism is that of an immune-mediated attack on hematopoietic stem cells (Resnik et al., 2008).

2.2. Myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders with an inherent tendency for leukemic transformation. Diagnosis is currently based on the presence of peripheral blood cytopenias, peripheral blood and bone marrow dysplasia/blasts, and clonal cytogenetic abnormalities. With the advent of next generation sequencing, recurrent somatic mutations in genes involved in epigenetic regulation (TET2, ASXL1, EZH2, DNMT3A, IDH1/2), RNA splicing (SF3B1, SRSF2, U2AF1, ZRSR2), DNA damage response (TP53), transcriptional regulation (RUNX1, BCOR, ETV6) and signal transduction (CBL, NRAS, JAK2) have been identified in myelodysplastic syndromes (Gangat et al., 2016).

Myelodysplastic syndromes are characterized by ineffective hematopoiesis with varying degrees of dysplasia and peripheral cytopenias. Myelodysplastic syndromes are supported by a tumorigenic and a proinflammatory marrow microenvironment. Current treatment strategies for lower-risk myelodysplastic syndromes are on improving quality of life and cytopenias, while prolonging survival and delaying disease progression for higher-risk myelodysplastic syndromes. Several promising drugs include hypoxia-inducible factor stabilizer roxadustat, telomerase inhibitor imetelstat, oral hypomethylating agents (CC-486), TP53 modulators (APR-246 and ALRN-6924), and the anti-CD47 antibody magrolimab. Targeted therapies approved for acute myeloid leukemia treatment, such as isocitrate dehdyrogenase inhibitors and

venetoclax, are also being studied for use in myelodysplastic syndromes (Saygin & Carraway, 2021).

2.3. Paroxysmal nocturnal hemoglobinuria

Absence of cell-surface complement inhibitors CD55 and CD59 is a proposed mechanism underlying the complement-mediated destruction of affected red blood cells in paroxysmal nocturnal hemoglobinuria patients, but Factor H, a fluid-phase complement inhibitor, was also proposed as involved (Zhang et al., 2021). Paroxysmal nocturnal is characterized by intravascular hemolysis, thrombosis and bone marrow failure. Prior to specific therapy, Paroxysmal nocturnal hemoglobinuria led to the death of around half of affected individuals, mainly through thrombotic complications. The anti-C5 monoclonal antibody eculizumab has revolutionized treatment, controlling intravascular hemolysis and thrombosis occurrence, with improved long-term survival (de Latour et al., 2022).

Paroxysmal nocturnal hemoglobinuria is a rare, acquired disease characterized by chronic complement-mediated hemolysis. C5 inhibition controls intravascular hemolysis in untreated Paroxysmal nocturnal hemoglobinuria but cannot address extravascular hemolysis. Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, potentially inhibits both intravascular and extravascular hemolysis. Pegcetacoplan was found superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with paroxysmal nocturnal hemoglobinuria by providing broad hemolysis control, including control of intravascular and extravascular

hemolysis in a study of Hillmen et al., (2021). The safety and efficacy of allogeneic hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria is still unclear (Nakamura et al., 2021).

2.4. Acquired amegakaryocytic thrombocytopenia

Amegakaryocytic thrombocytopenia is a severe form of thrombocytopenia with reduced or absent megakaryocytes in the bone marrow. It can be congenital or acquired. Congenital amegakaryocytic thrombocytopenia is a rare, severe form of thrombocytopenia with reduced or absent megakaryocytes in the bone marrow since birth, especially seen in the neonatal period (Khincha & Savage, 2016). Standard treatment strategy has not been established for acquired amegakaryocytic thrombocypenia which is extremely rare (Tian et al., 2021).

Acquired amegakaryocytic thrombocytopenia is a bleeding disorder that causes severe thrombocytopenia with preserved hematopoiesis of other cell lineages. Many cases are misdiagnosed and treated as immune thrombocytopenia (Roy et al., 2020). Distinguishing "Acquired amegakaryocytic thrombocytopenia" from "Immune thrombocytopenia" is important as the outcome and response to therapy strongly change. Aplastic anemia can occur in the follow-up but rarely. Corticosteroids and intravenous immunoglobulins are inefficient in most cases, ciclosporin appear to be very effective, thrombopoietin receptor agonists can also be an option, as single therapy or in associations (Roeser et al., 2021).

3. Conclusions

Significant advances in scientific knowledge and understanding of pathogenesis can be obtained from studying rare diseases in children. Studies on rare syndromes provide insights into the normal physiology at both the cellular and global levels.

Human leukocyte antigen identical hematopoietic stem cell transplantation is the best treatment for Fanconi anemia. Patients with dyskeratosis congenita are at increased risk of marrow failure, myelodysplastic syndrome, acute myelogenous leukemia and pulmonary fibrosis. Identification of Nemo-like kinase is a potential target for Diamond Blackfan Anemia therapy. Allogeneic hematopoietic stem cell transplantation is a curative procedure in patients with Shwachman–Diamond syndrome with bone marrow abnormalities. The main causes of severe congenital neutropenia are autosomal dominant mutations in the "elastase neutrophil expressed" (ELANE) gene that lead to a block in neutrophil differentiation. Drugs, environmental toxins, viruses, and ionizing radiation were reported as causally associated with acquired aplastic anemia. Targeted therapies approved for acute myeloid leukemia treatment, such as isocitrate dehdyrogenase inhibitors and venetoclax, are also being studied for use in myelodysplastic syndromes.

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CHAPTER 3

MATERNAL OBESITY AND ASSOCIATED RISKS AT PREGNANCY: A REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSIS

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1. Introduction

Overweight or obese pregnant women number is rapidly increasing. Combination of decreased insulin sensitivity and obesity increase the risk of metabolic syndrome and associated problems of hypertension, diabetes, cardiovascular disorders and hyperlipidemia in long term. There are significant changes in the microbiome during pregnancy during dramatic metabolic and immunological changes and weight gains occur. Gestational diabetes, gestational hypertension, pre-eclampsia, depression, caesarean and instrumental birth, and surgical site infection are more occur in pregnants with obesity compared to healthy weight women. Maternal obesity during pregnancy is also associated with diverse adverse outcomes for offspring later in life. Actions to prevent, manage and treat obesity during pregnancy is costly. Health services should understand health benefits and cost savings may occur by reduction the problem.

Here in this review, reader may find a review of systematic reviews and meta-analysis published after 2010 on maternal obesity and associated risks at pregnancy.

Maternal obesity, excessive gestational weight gain and post-partum weight retention are new public health challenges, due to their association with short- and long-term maternal and neonatal negative outcomes (Farpour-Lambert et al., 2018). The proportion of overweight women (body mass index 25-30 kg/m2) or obese (body mass index >30 kg/m2) who become pregnant is rapidly increasing (Molyneaux et al., 2014). These women are under higher risk for a decreased insulin

sensitivity compared to average weight women. Combination of decreased insulin sensitivity and obesity increase the risk of metabolic syndrome and associated problems of hypertension, diabetes, cardiovascular disorders and hyperlipidemia in long term. Due to metabolic alterations at normal pregnancy, 60% decrease in insulin sensitivity increase risk of metabolic dysregulation in pregnancy (gestational diabetes, fetal overgrowth and preeclampsia) for obese and overweight women. So pregnancy can be a metabolic stress test for the risk of the metabolic syndrome in future (Catalano, 2010).

Approximately 1/3 of women at childbearing age are overweight or obese and pregnancy is increasing risks also for the children of these women (Stubert et al., 2018). Pregnancy is a period with wide physiological stress on the fetus (Sahay & Nagesh, 2012).

Maternal obesity is the most common risk factor for maternal mortality in developed countries and associated with a spectrum of adverse pregnancy outcomes. It may have long term implications for the mother and infant health, which also have economic implications. Actions to prevent, manage and treat obesity during pregnancy is costly. Health services should understand at what cost the problem can be reduced and then, what health benefits and cost savings will occur in future by reduction the problem (Rowlands et al., 2010).

2. Systematic Reviews and Meta-Analysis

2.1. Mother

To learn more on the effect of pre-pregnancy obesity and excess gestational weight gain association with pregnancy complications,

caesarean delivery, preterm birth, placenta weights and longer postnatal hospital stay, Mamun et al., (2011) used info of 6.632 women who gave birth in Australia between 1981-1983. They found that obese women prior to pregnancy and excess weight gained women during pregnancy were at higher risk for a pregnancy complication, caesarean section, increased birth weight difference, increased placental weight difference and longer stays in hospital. Also mothers gained inadequate weight or underweight before pregnancy were at higher risk for preterm birth, lower risk for pregnancy complications and have lower birth and placental weights. Excess gestational weight gain was associated with longer stay in hospital after delivery, independent of pre-pregnancy body mass index, pregnancy complications and caesarean delivery. In addition to pre-pregnancy obesity, it is vital that clinical practice considers excess gestational weight gain as another indicator of adverse pregnancy outcomes.

Recent microbiome researches revealed multiple roles of microorganisms of human body in host metabolism, immunity and health. Diversified physiological and pathological states, such as obesity and metabolic syndrome, correlates with microbial changes termed dysbiosis. Our microbiomes change in response to our environment, hormones, weight, diet and other factors. There are significant changes also in the microbiome during pregnancy during dramatic metabolic and immunological changes and weight gains occur (Neuman & Koren, 2017).

New studies and a large meta-analysis were reported that weight reduction strategies were not associated with adverse maternal or perinatal outcomes. Suggestions proposed that an approach of dietary modification alone can achieved with reductions in gestational weight gain (Khan, 2012).

Analysis of 22 reviews showed that the gestational diabetes, gestational hypertension, pre-eclampsia, depression, caesarean and instrumental birth, and surgical site infection are more occur in pregnants with obesity compared to healthy weight women. Preterm birth, large-for-gestational-age babies, congenital anomalies, foetal defects and perinatal death were also linked with higher risk of maternal obesity. Breastfeeding initiation rates were lower and there was greater risk of early breastfeeding cessation in obese women compared to healthy weight women. These outcomes result with longer hospital stays. Obese women need support to lose weight before they conceive and to minimize weight gain during pregnancy (Marchi et al., 2015).

Antenatal and postpartum mental disorders among obese and overweight women were assessed by review of 62 studies by Molyneaux et al., (2014). Studies covered 540.373 women. Obese and overweight women showed significantly elevated depression symptoms than normal-weight women both during pregnancy and postpartum. Antenatal anxiety was also higher for obese women. A few of the studies identified increased risk for postpartum anxiety, eating disorders or serious mental illness among obese women. Healthcare providers should be aware that obese when pregnant women are more

likely to experience elevated antenatal and postpartum depression symptoms than normal-weight women, with intermediate risks for overweight women.

Obesity and anxiety during the perinatal period are common and associated with poor health outcomes for the mother and the child. Nagl et al., (2015) reviewed the association between anxiety and obesity during the perinatal period. 70% of the analysed studies reveal a positive association between two. Most of the analysed studies suggested that obese pregnants might be vulnerable for comorbid anxiety and require targeted psychological support.

Gaillard et al., (2016) discussed results from recent studies examined the influence of maternal obesity at pregnancy on fetal outcomes and childhood adiposity, cardio-metabolic, respiratory and cognitive-related health outcomes. Studies strongly suggested that maternal pre-pregnancy obesity and excessive gestational weight gain were associated with elevated risks of fetal pregnancy complications and adverse childhood respiratory, cardio-metabolic and cognitive-related health outcomes. It is unclear if these associations were due to intrauterine mechanisms or explained by confounding family-based sociodemographic, genetic factors and, lifestyle.

Farpour-Lambert et al., (2018) reviewed effective lifestyle interventions to manage weight and improve maternal and infant outcomes during pregnancy and postpartum. For healthy women from all body mass index classes: diet and physical activity interventions can decrease gestational weight gain, risks of gestational weight gain above

the "Institute of Medicine" guidelines, pregnancy-induced hypertension, cesarean section and neonatal respiratory distress syndrome without any maternal/fetal/neonatal adverse effects. For women with overweight/obesity: multi-component interventions can decrease gestational weight gain, pregnancy-induced hypertension, macrosomia and neonatal respiratory distress syndrome. Diet was associated with bigger reduction of risks of gestational diabetes mellitus, pregnancy-induced hypertension and preterm birth when compared to any other intervention. After delivery, combined diet and physical activity interventions reduce post-partum weight retention in women of any body mass index or with overweight/obesity, but no other effects were reported. Approaches with multi-components including balanced diets with low glycaemic load and light to moderate intensity physical activity, 30–60 min per day 3–5 days per week, should be recommended from the first trimester of pregnancy and maintained during the postpartum period.

Yao et al., (2020) performed random effect meta-analysis to evaluate the relationship between central obesity and risk of gestational diabetes mellitus. 11 cohort studies with an overall sample size of 27.675 women and 2.226 patients with gestational diabetes mellitus were included in their analysis. Thier findings indicate that the risk of gestational diabetes mellitus was positively associated with maternal central obesity.

Multiparity, age and high body mass index are widely investigated factors related to urinary incontinence during pregnancy. Cohort, case-

control or cross-sectional studies were used by Barbosa et al., (2018) for multivariate analysis. Very low quality of evidence shows that multiparity, age 35 years or older and overweight and obesity during pregnancy are risk factors for urinary incontinence in pregnancy.

2.2. Offspring in relation with mother

Pre-pregnancy overweight and obesity, birth weight and offspring overweight and obesity data were extracted by Yu et al., (2013) from published 45 studies. It was determined that pre-pregnancy underweight is increasing the risk of small-for-gestational age and low birth weight; pre-pregnancy overweight and obesity is increasing the risk of large-for-gestational-age, high birth weight, macrosomia and subsequent offspring overweight and obesity.

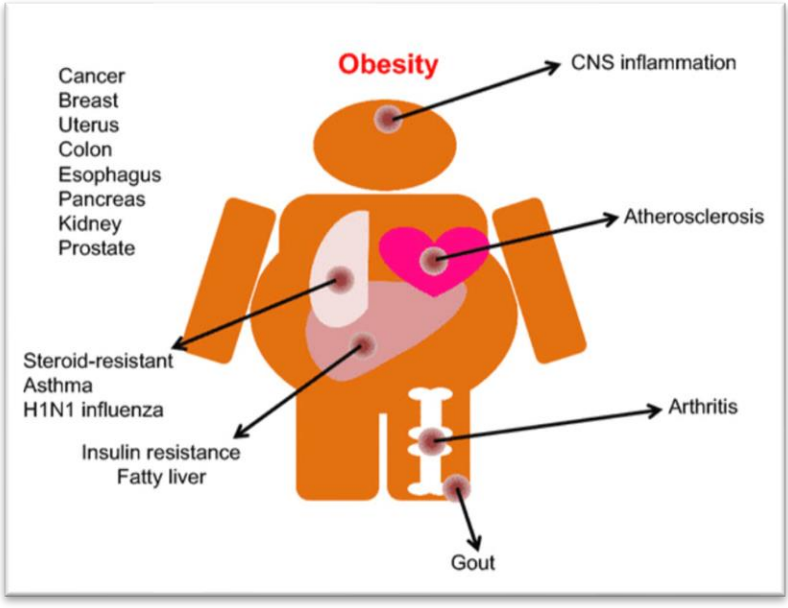

Fig. 1. Obesity-associated diseases (Endo et al., 2017).

Maternal obesity during pregnancy is also associated with diverse adverse outcomes for offspring later in life. Obesity in pregnancy may be associated with central nervous system problems in the foetus and newborn. Van Lieshout et al., (2011) systematically reviewed studies to see associations between maternal overweight and obesity during pregnancy and cognitive, behavioural and emotional problems in offspring. Study suggested that the offspring of obese pregnancies may be at increased risk of cognitive problems and symptoms of attention deficit hyperactivity disorder in childhood, eating disorders in adolescence and psychotic disorders in adulthood. Lau et al., (2014) systematically reviewed the evidence from prospective and retrospective cohort studies on the association between gestational weight gain and offspring's body weight. Findings suggested that gestational weight gain is a potential risk factor for childhood obesity.

Kominiarek & Chauhan, (2016) compared national guidelines' approach to the management of obesity in women. All guidelines highlighted a higher risk for miscarriage, gestational diabetes, birth defects, fetal growth abnormalities, hypertension, cesarean sections, postpartum hemorrhage, difficulty with anesthesia, and obesity in offspring. Counseling on the obesity risks and weight loss before pregnancy were universal recommendations. There were substantial differences in the recommendations on the gestational weight gain goals, nutrient supplements, vitamin supplements, screening for gestational diabetes and thromboprophylaxis among the guidelines.

Obesity before and during pregnancy leads to decreased offspring cardiometabolic health. Menting et al., (2019) performed meta-analyses and subgroup analyses to systematically review animal experimental evidence on maternal obesity before and during pregnancy and offspring anthropometry and cardiometabolic health. Offspring of mothers with obesity had higher systolic blood pressure, body weight, triglycerides, fat percentage, total cholesterol, insulin level and glucose level compared to offspring of control mothers, but similar birth weight. Sex, age, or species did not influence the effect of maternal obesity on cardiometabolic health of offsprings. Obesity before and during pregnancy reduced offspring cardiometabolic health in animals.

Maternal obesity makes an extra demand for health services, as routine obstetric care requires alterations for obese women of childbearing age. Maternal gestational smoking, alcohol drinking, diabetes and pre-pregnancy obesity are thought to elevate the risk of cryptorchidism in newborn males, but evidence is inconsistent. Zhang et al., (2015) conducted a review and meta-analysis of studies on the association between maternal gestational alcohol drinking, smoking, diabetes, and pre-pregnancy obesity and the risk of cryptorchidism. Maternal gestational smoking, but not maternal pre-pregnancy overweight or obesity was found associated with increased cryptorchidism risk for the offspring.

3. Conclusions

Gestational diabetes, gestational hypertension, pre-eclampsia, depression, caesarean and instrumental birth, and surgical site infection

are more occur in pregnants with obesity compared to healthy weight women. Maternal obesity during pregnancy is also associated with diverse adverse outcomes for offspring later in life. Actions to prevent, manage and treat obesity during pregnancy is costly.

Maternal obesity makes an additional demand for health-care services, as the routine obstetric care pathway requires alterations to ensure the most optimal care for obese women of childbearing age.

Only limited guidance on maternal obesity and gestational weight gain exists. International, evidence-based guidelines on the management of maternal obesity and excessive gestational weight gain should be developed to reduce the associated health-care and economic costs.

A potential effect modification by maternal age, ethnicity, gestational weight gain, as well as the role of gestational diseases should be addressed in future studies.

Future intervention studies should investigate whether reducing obesity prior to conception could prevent these detrimental programming effects and improve cardiometabolic health of future generations.

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CHAPTER 4

FAMILY HEALTH NURSING: A RECENT REVIEW

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1. Introduction

Nurses remain at the forefront of patient care (Maharaj et al., 2019) and are among the largest home care services providers. Thus workforce optimisation of nurses positively influence patient outcomes (Ganann et al., 2019). In many countries in the world, nursing discipline and profession has been strengthened by strong and effective leaders in education, research and clinical practice. The 72nd World Health Assembly designated year 2020 as "International Year of the Nurse and the Midwife" for contributions of nurses and midwives to the global health and well-being (Daly et al., 2020). Family nursing is an essential part of nursing (Huang et al., 2021). Family nurse practitioners significantly contribute to disease management and health promotion in primary care (Tsay et al., 2021). Implementing family system nursing in clinical settings is rising (Svavarsdottir et al., 2018).

Importance of human resource planning in home healthcare is increasing everyday due to serious degree of nurse and caregiver shortages in companies in many countries (Demirbilek et al., 2021). Professional nursing is assisting people during health and disease. They are shaping self-care capabilities of people. Complexity of tasks puts responsibilities on nurses due to direct contact with patients, families and communities (Kecka, 2019). Studies of family nursing interventions have shown positive results for the health of individuals and families (Rodrigues et al., 2021). A nurse's skill in establishing therapeutic communication is central to family nursing. Using a family-centered approach, nurses can facilitate relationship building with

members of a family unit (O'Rae et al., 2021). Systems thinking is essential for advanced family nursing practice, yet this skill is complex and not innate (Looman, 2020).

Family nurse practitioners have a plethora of employment options upon graduation. Besides primary care, many are working in nontraditional settings such as urgent care, emergency departments, retail health, and specialty practices. In many of these settings, practitioners are required to perform procedures (Woroch & Bockwoldt, 2021). Patients, their families and nursing professionals benefit from applying the family nursing theory to practice. But implementation of family nursing in clinical practice is limited partially due to insufficient or inadequate educational programs focused on family nursing (Gutierrez-Aleman et al., 2021). Increasing number of individuals receive care at home but significant ratio of these patients acquire infections during their care period. Whilst there has been significant focus on strategies for infection prevention and control in acute care environments (Dowding et al., 2020). Researchers have found that many primary care providers are not following developmental screening recommendations (Gellasch, 2019). Although the nursing profession has ample knowledge about the importance of family nursing and the value of family-focused actions, there is a lack of curricular and teaching models that address nursing practice with families in numerous courses and learning experiences (Meiers et al., 2018).

The demand for primary care providers in developed countries is rising and shortages by 2025 are projected. Nurse practitioners are key to

addressing the current and future shortage of health care providers, especially in primary care. However, nurse practitioners face a significant challenge when transitioning from the registered nurse role to the advanced practice role, which can affect job satisfaction and retention (Finneran & Kreye, 2021). Health care and services in the west are mostly oriented towards individuals, and the needs of families often receive little consideration (Gervais et al., 2020).

Countries with ageing populations seek to reduce professional and residential care and therefore encourage family caregiving. Intensive family caregiving, however, places families at risk for caregiver burden which may lead to increased professional care and admission into residential care (Broekema et al., 2021).

Family plays an important role in health and illness, and preparing the nurses to assess and improve the family functioning and relationship based on a theoretical framework is of critical importance (Yektatalab et al., 2017). There is increasing focus on collaboration in primary health care, but there is insufficient patient perspective on collaboration between the family nurse and family doctor. The traditional model of nursing care and the hierarchical relationship, in which the doctor has the dominant role, are evident in the patients' remarks. The autonomy of nursing could be strengthened by expanding, and highlighting, the primary care activities that a nurse can perform on her own (Taranta & Marcinowicz, 2020).

Alcohol and substance-related disorders affect individuals throughout the global community. It is important that nurse practitioners

understand the use of screening, brief intervention, and referral to treatment in recognizing these disorders before development of chronic disease conditions (Arends et al., 2021).

A nurse home visitation programme in the USA was found to improve a wide range of outcomes for teenage mothers and their children (Cavallaro et al., 2020). Health care provider support is essential for breastfeeding success. Family Nurse Practitioners are in a unique position to promote and manage breastfeeding (Webber & Serowoky, 2017).

Six main categories of qualities define a "good family nurse" meaning to older patients. These are: 1) Personal traits and attributes (gender and individual characteristics and behaviours not directly related to nursing). 2) Providing care (caring attitude and patient support). 3) Communicating with the patient (the ability to listen and inform the patient). 4) Professional competence (knowledge, professional experience and good technical skills). 5) Ethical attitude (respect, patience and vocation). 6) Availability (the frequency and duration of home visits, organization of the doctor's appointments) (Marcinowicz & Taranta, 2020).

Nurse practitioners are expected to fill gaps in providing primary care and need vital skills to meet the growing need for primary care providers. One necessary skill is managing "on-call" clinical questions/concerns by patients across the life span (Conelius et al., 2019).

2. Family

Nursing home residents frequently experience heavy and unnecessary care transitions towards the end of life. Families have a significant role in emergency department transfer decisions as they see the change of condition as a crisis. This crisis sense is driven by four major influences: 1) insecurities with nursing home care; 2) being not prepared for end of life; 3) absent/inadequate care planning; 4) deficit of communication and agreement within families related to care goals (Stephens et al., 2015). A serious illness may effect family system and members of family frequently experience considerable physical, emotional and social burdens (Widiyanto et al., 2021).

The loss of sense is the core of the moral pain for families, nursing staff and old patients. Sense is a part of person-centered care quality in a nursing home, for residents, their family, and the nursing staff quality of life at work. Possible misunderstanding or even conflicts may appear. Medical doctors, nurse-managers and psychologists can bridge the gap between the semiospheres (Thomas et al., 2016).

Family members freqently rely on health care workers to guide and support decision-making process. Emotional consideration is commonly acceptable in decision-making (Itzhaki et al., 2016). The heart of social systems is the family and if we are to maintain the health of societies, we need to discover the best means of nurturing the heart (Smith, 2015).

Patients generally prefer to have their family present during medical or nursing interventions. Family presence is assumed to reduce anxiety, especially during painful interventions (İşlekdemir & Kaya, 2016).

High-quality palliative care for people with dementia should be patient-centered, family-focused, and include well-informed and shared decision-making, as affirmed in a recent white paper on dementia from the European Association for Palliative Care (Penders et al., 2015). The behavioral symptoms that often accompany dementia (for example, pacing, calling out, and resistiveness) are stressful to carers and greatly increase the risk of institutionalization. While psychotropic medications are commonly prescribed, their efficacy is limited (Van der Ploeg et al., 2016).

are for people with advanced dementia requires a palliative approach targeted to the illness trajectory and tailored to individual needs. However, care in nursing homes is often compromised by poor communication and limited staff expertise (Agar et al., 2015).

Family nurse practitioner graduates must be prepared to care for individuals and families and to demonstrate a commitment to family-centered care. family nurse practitioner educators are challenged to translate theoretical frameworks into meaningful clinical engagement through novel teaching strategies that promote family-centered care in a health care environment that focuses primarily on the individual (Ellis et al., 2015).

Research supporting use of standardized patients in health professional education is strong. Evidence suggests integrating the use of standardized patients into clinical training provides learners with interactive practice in gaining and perfecting clinical skills, in becoming competent in communication skills for provision of health care, and results in improved satisfaction for faculty and students (Pastor et al., 2015).

Communication is one of the key principles in family centered care. Studies have shown some drawbacks in communication between families and nurses. Identification of the obstacles against nurse-family communication helps managers of healthcare systems to plan and eliminate the challenges of effective communication. Besides, elimination of these factors (inadequate education, poor professionalization, difficult working conditions, authoritarian management) leads to appropriate strategies for effective application of family centered care (Shirazi et al., 2015).

The next decade is likely to produce any number of global challenges that will affect health and health care, including pan-national infections such as the new coronavirus Covid-19 and others that will be related to global warming. Nurses will be required to react to these events, even though they will also be affected as ordinary citizens. The future resilience of healthcare services will depend on having sufficient numbers of nurses who are adequately resourced to face the coming challenges (Catton, 2020). Nursing shortages, particularly in critical care units, are a major concern worldwide. Job satisfaction is a key

factor associated with the high turnover of critical care nurses (Dilig-Ruiz et al., 2018).

3. CONCLUSIONS

Family members freqently rely on health care workers to guide and support decision-making process. There is a lack of curricular and teaching models that address nursing practice with families in numerous courses and learning experiences. Integrating the use of standardized patients into clinical training provides learners with interactive practice in gaining and perfecting clinical skills. Increasing number of individuals receive care at home but significant ratio of these patients acquire infections during their care period. Nursing home residents frequently experience heavy and unnecessary care transitions towards the end of life. Family nurse practitioner graduates must be prepared to care for individuals and families and to demonstrate a commitment to family-centered care. Communication is one of the key principles in family centered care. Job satisfaction is a key factor associated with the high turnover of critical care nurses

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CHAPTER 5

ROLE OF PUBLIC HEALTH NURSING DURING COVID-19

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1. INTRODUCTION

Public health emergencies are serious social problems, threatening people's lives, causing considerable economic losses, and related to all mankind life and health and safety. Nurses are essential in the fight against the public health emergency (Xu et al., 2021). The Covid-19 pandemic has presented an international health crisis in our lifetime. While much attention has been paid to health workers in critical care and acute areas, nurses working outside of hospitals are also significantly affected (Halcomb et al., 2020). The pandemic highlighted the importance of a strong, effective public health nursing workforce (Cygan et al., 2021). During times of crisis, nurses are dynamic, innovative, and crucial forces for health equity (DeGroot et al., 2021).

Nurses have to ensure that all patients acquire personalized, high-quality services irrespective of their infectious condition. They will also engage in planning for anticipated Covid-19–related outbreaks, which increase the demand for nursing and healthcare services that might overload systems. Moreover, nurses must maintain effective supply and usage of sanitation materials and personal protective equipment and offer screening information, confinement guidelines, and triage protocols based on the latest guidance (Fawaz et al., 2020).

The role of nurse changes as the health care is needed in the hospitals, society or community. Nurses are providing essential health care services throughout the health care system. In response to Covid-19 pandemic, the role of nurse changes to care or respond to the needs of the patients, their families and their caregivers. They also should take

part in policies making, doing procedures and taking care of necessary supply of the material and equipment in the hospitals (Sharma et al., 2020).

With the daily number of confirmed Covid-19 cases and associated deaths rising exponentially, social fabrics on a global scale are being worn by panic, uncertainty and fear. Comprising more than half of the global health care workforce and the highest proportion of direct patient care time than any other health professional, nurses are at the forefront of this crisis. Throughout the evolving Covid-19 pandemic, nurses will increasingly exercise their expertise in symptom management, ethics, communication, end-of-life care and other skills (Rosa et al., 2020).

The essential functions of a school nurse during pandemic of the coronavirus disease 2019 is uniquely prepare them to ensure population health. In addition to both individual and population health within the school setting, school nurses are effective partner in emergency planning and can help inform decision making and policy making within communities (Flaherty, 2020). Globally, children have been profoundly affected by the Covid-19 pandemic in many ways. While the majority of children with acute Covid-19 infection experience mild illness and fully recover, many go on to experience long Covid. Long Covid is clinically identified by experience of persistent symptoms for several months after the acute infection (even in children who were asymptomatic). There is currently no agreed consensus on the case definition of long Covid, but real-world data from American health insurance firms and the Unite Kingdoms Office for National Statistics

report that children may experience intestinal symptoms, pain, breathlessness, cognitive dysfunction and post-exercise malaise. The current understanding of the natural history, diagnostics and treatments of long Covid is limited, meaning the medical model in isolation is not helpful. Health visitors and school nurses are ideally placed to case-find children with long Covid and co-produce child and family-centred care (Fanner & Maxwell, 2021).

In the situation of scaled-down community health and social services during the Covid-19 outbreak, the community nursing team adopted measures for pandemic preparedness. Structured teleconsultation and technology advancement are useful to complement the service (Yi et al., 2020).

Residential and nursing care patients are considered highly vulnerable to the coronavirus due to their physical needs and environmental factors. Significant concern was raised with personal protective equipment availability and appropriate training and support in local care homes (Murphy, 2021). Providing person-centred end-of-life care at home and in care homes during the Covid-19 pandemic has been challenging. These challenges extend beyond the interpersonal communication barriers created by wearing personal protective equipment for infection control. Visors and facemasks make it harder to hear soft voice tones or read facial expressions, which are key tools in empathetic communication. The pandemic has imposed massive stress on care resources. New models of care delivery have also created opportunities for nurses supporting people in community settings to

develop their role and skills. Nurses working in the community have acquired newly extended roles (Bowers et al., 2021).

Primary healthcare services are playing a critical role in meeting increased need for end-of-life care in the community during the Covid-19 pandemic. They have adapted rapidly, but the significant emotional impact, especially for community nurses, needs addressing alongside rebuilding trusting and supportive team dynamics (Mitchell et al., 2021).

Nurses also play a key role in providing public education on disease prevention and reducing the spread of misinformation around the outbreak. There has been widespread misinformation on how Covid-19 is transmitted, who is at risk of transmitting or receiving the virus and where outbreaks are occurring (Choi et al., 2020).

Nurse should familiar with scientific updates of Covid-19 disease. The nurses should to know and review the triage policies and procedures of their organization and follow the same in response to Covid-19. The nurse role in triage is not to diagnose, but to recognize or identify the patients for separation or isolation if suspected to have Covid-19. Provide psychological support to the patients and family, to help them to alleviate fear, anxiety and depression about the Covid-19. Explain to the patient, family and caregivers about the causes, risk, management and prognosis of Covid-19, so they can participate in the treatment plan (Sharma et al., 2020).

During pandemic, role of public health nurses are:

- Collaborating with other healthcare organizations to provide information on Covid-19 and nonpharmaceutical interventions.
- Reassuring residents that fears are valid, but that panic should be avoided.
- Offering the flu vaccine.
- Providing education about prevention.
- Working with local government to review and improve emergency operations plans.
- Engaging key stakeholders to help support Covid-19 preparation efforts.
- Exploring how to support the needs of employees and high-risk populations in communities.
- Developing plans to support homeless individuals, a highly vulnerable population (Papadimos et al., 2020).

2. Nursing homes

Almost half of deaths related to Covid-19 in the United States are linked to nursing homes. Upon detection of confirmed cases within the facility, each nursing home in collaboration and consultation with local hospital, public health officials, and parent corporation implemented immediate facility-wide testing and the following intervention measures: cohorting of Covid-19 positive residents; communication regarding testing and results with residents, healthcare professionals, and families; personal protective equipment reeducation and use throughout facilities; and dedicated staffing for infected patients cohorted in a dedicated Covid-19 wing (Montoya et al., 2021).

Nursing homes in California with low registered nurse and low total staffing levels appear to leave residents vulnerable to Covid-19 infections. Establishing minimum staffing standards could prevent this in the future (Harrington et al., 2020).

Throughout the pandemic, long-term-care facility deaths made up over a third of all US deaths based on Covid Tracking Project data, which includes nursing homes, assisted living and other long-term care facilities. The Center for Medicare & Medicaid Services only reports data for nursing homes, where a quarter of deaths in the US occurred. The impact on these communities is likely higher than this figure shows because of missing historical deaths from both state and Medicare & Medicaid Services data, and inconsistent, non-standardized reporting by states (Quinn et al., 2021).

3. CONCLUSIONS

During pandemic, role of public health nurses are: 1) Collaborating with other healthcare organizations to providing information on COVID-19 and nonpharmaceutical interventions. 2) Reassuring residents that fears are valid, but that panic should be avoided. 3) Offering the flu vaccine. 4) Providing education about prevention. 5) Working with local government to review and improve emergency operations plans. 6) Engaging key stakeholders to help support COVID-19 preparation efforts. 6) Exploring how to support the needs of employees and high-risk populations in communities. 7) Developing plans to support homeless individuals, a highly vulnerable population.

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CHAPTER 6

NATURE OF KIDNEY STONE DISEASES: A REVIEW

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INTRODUCTION

The incidence and prevalence of kidney stones was increased during past four decades. Aetiology of kidney stones is multifactorial (environmental, hormonal, dietary and genetic). The prevalence peaks at 40–60 years. Kidney stone formation pathogenesis has multiple steps including complex interactions between protein matrix and mineral components. Component of stones are calcium oxalate, calcium phosphate, infection stone, uric acid stone and cystine. Urinary stone disease has associations with antibiotic-driven shifts in the microbiome.

Here in this review, some information from latest articles published on kidney stone diseases are summarised.

Kidney stones (also known as urinary stones) are mineral deposits in the renal calyces and pelvis that are found free or attached to the renal papillae. They contain crystalline and organic components and are formed when the urine becomes supersaturated with respect to a mineral. Calcium oxalate is a major constituent of most stones, which form on calcium phosphate named Randall's plaques present on renal papillary surface. Stone formation is very widespread (Khan et al., 2016). Kidney stones are affecting approximately 10% of adults globally and its incidence is increasing. Kidney stone forms as a result of imbalance of crystallization inhibitors and promoters. Calcium-containing calculi represent approximately 80% of stones. Underlying aetiology for most patients is multifactorial (environmental, hormonal, dietary and genetic) (Singh et al., 2021). Kidney stone disease (nephrolithiasis) has a heritability of 45–60%. It is a major clinical and

economic health burden (Howles et al., 2019). About 80% of kidney stones are composed of calcium oxalate (CaOx) and variable amounts of calcium phosphate. Hyperoxaluria is an important factor for CaOx nephrolithiasis but underlying metabolic mechanisms of CaOx nephrolithiasis is still not defined (Gao et al., 2016).

The incidence and prevalence of kidney stones was increased during past four decades. Diagnosis range from incidental asymptomatic finding to multiple painful episodes of ureteral obstruction with eventual kidney failure. Higher attention to kidney stone classification, approaches to assess the risk of recurrence and prevention strategies can improve clinical care. There is a lack of a standardized stone classification system which may improve study and care of stone formers (Thongprayoon et al., 2020). Many studies shown that male patients with uric acid nephrolithiasis outnumber female patients. Low urine pH, impaired renal function, and gout are the mediators for the development of uric acid nephrolithiasis in males. Treatment and follow-up of kidney diseases, acidic urine, and uric acid metabolism disorders should be considered in males with uric acid nephrolithiasis (Chen et al., 2018). In the study of Zhang et al., (2021) total 1520 patients of urinary stones formation from China were analysed. They determined that the most common component of stones were calcium oxalate (77%), followed by calcium phosphate (9%), infection stone (8%), uric acid stone (5%) and cystine (1%). Calcium oxalate stones were more frequent at males, while infection stone and cystine stones were more frequent in females. The prevalence was peaked at 41–60 years in both women and men. Uric acid stones occurred frequently in

patients with lower urinary pH. Alkaline urine, neutral urine and urinary infection were more associated with infection stone type stones. High serum creatinine levels were more likely to develop uric acid stones. Uric acid stone proportion in diabetics was higher and hypertension incidence was higher in uric acid stones patients. Calcium oxalate stones were more frequent in kidneys and ureters. Struvite stones were more frequent in the lower urinary tract.

Most of urinary stones in humans are mainly composed of crystalline calcium salts but other metals and nonmetals exist with concentrations 10 orders of magnitude. Elements' contribution other than calcium on formation, recurrence or shapes of human urinary stones is poor-defined. Amount of some elements within human calcium-based urinary stones does not correlate with their normal urinary concentrations. This may be due to accumulation or other processes affecting elemental composition of stones (Ramaswamy et al., 2015).

Nephrolithiasis (Kidney stone disease)

Kidney stone disease is a complex disorder with a strong genetic component (Oddsson et al., 2015). Etiology of kidney stone disease is heterogeneous, range from monogenic defect to complex interactions of environmental and genetic factors (Nettuwakul et al., 2020). Kidney stone formation pathogenesis has multiple steps including complex interactions between protein matrix and mineral components. Calcium-binding proteins have big effect on kidney stone formation. Spatial distributions of these proteins in kidney stones are essential for evaluating the in vivo effects of proteins on the stone formation (Tanaka

et al., 2021). Nephrolithiasis can be associated with urinary solute composition alterations including hypercalciuria. Prevalence of monogenic kidney stone disorders, including renal tubular acidosis with deafness, primary hyperoxaluria, Bartter syndrome and cystinuria, in patients attending kidney stone clinics is approximately 15%. Genetic influence on stone formation in these idiopathic stone formers remains considerable with an estimated heritability of >50% for hypercalciuria and >45% for nephrolithiasis. Genome-wide associations indicate that several genes and molecular pathways contribute to stone formation risk. Genetic approaches, studying both monogenic and polygenic factors in nephrolithiasis revealed important roles (ions, protons and amino acids; transporters and channels; calcium-sensing receptor signalling pathway; metabolic pathways for vitamin D, oxalate, purines, cysteine and uric acid) in the aetiology of kidney stones (Howles & Thakker, 2020).

Relation with microbiome

Factors driving the rapidly rise of urinary stone disease prevalence is unknown. Microbiome studies propose that dysbiosis may partially contribute to this increase. Microbiome and metabolic results on higher rates of antibiotic use among urinary stone disease patients support the hypothesis that urinary stone disease is associated with an antibiotic-driven shift in the microbiome. Specifically, urinary tract *Lactobacillus* and *Enterobacteriaceae* have protective and pathogenic roles for urinary stone disease, respectively. Antibiotics usage result with a long-term shift in microbiome which may increase urinary stone disease risk

(Zampini et al., 2019). Many metagenome-wide association studies for urolithiasis led to the discovery of interactions between urolithiasis and microbiome (Kachroo et al., 2021).

Escherichia coli is the most common bacterium isolated from urine and stone matrix of calcium oxalate stone formers (Amimanan et al., 2017). Individuals with kidney stones have a unique gut microbiome compared with those without kidney stones (Kelsey, 2016). Hyperoxaluria sa a result of endogenously synthesized and exogenously ingested oxalates is a main cause of recurrent oxalate stone formations. Humans mostly rely on gut microbiota for oxalate homeostasis. Suryavanshi et al., (2016) determined that higher than usual concentration of oxalate was found inhibitory to many gut microbes, including *Oxalobacter formigenes*, an oxalate metabolizing bacterial species. Concomitant enrichment of acid tolerant pathobionts in recurrent stone sufferers was also observed. Specific enzymes participating in oxalate metabolism were found augmented in stone endures. Additionally, hyperoxaluria driven dysbiosis was found to be associated with oxalate content, stone episodes and colonization pattern of *Oxalobacter formigenes*.

Stones

Kidney stone researches indicates critical roles of a protein group (named as ‘stone modulators’) in inhibition or promotion of stone formation (Sassanarakkit et al., 2020). Claudins are tight junction proteins regulating paracellular transport of solutes across epithelial layers. Role of cation-selective protein claudin 2 in regulating proximal

tubule calcium reabsorption and the formation of kidney stones was demonstrated (Allison, 2020).

Calcium oxalate kidney stones undergo cycles of repeated crystallization, dissolution, fracturing and faulting (Sivaguru et al., 2020). Data from an emerging transdisciplinary field integrating geology, biology and medicine (GeoBioMed) showed that kidney stone formation is controlled by the same fundamental sequence of processes that governs phosphate, carbonate and silicate deposition in other natural and engineered environments on Earth. These are known as universal biomineralization and diagenetic phase transitions. None of human kidney stone is 100% purely one mineral. They are classified as 'apatite', calcium oxalate dihydrate, calcium oxalate monohydrate (CaOx) and are composed of multiple mineralogical components comprising the continuum of diagenetic phase transitions from which they formed including amorphous calcium phosphate, hydroxyapatite, calcium oxalate dihydrate and calcium oxalate monohydrate. Amorphous calcium phosphate and hydroxyapatite spherules grow, cluster and coalesce to form euhedral calcium oxalate dihydrate crystals with planar concentric zoning and sector zones, indicating disequilibrium precipitation from supersaturated urine. Amorphous calcium phosphate, hydroxyapatite, calcium oxalate dihydrate and calcium oxalate monohydrate nanolayering and cross-cutting crystalline relationships (for example, dissolution voids, fracturing and faulting) record a complete stratigraphic record and paragenetic sequence that is analogous to natural and engineered biomineralization and diagenetic phase transition systems, the only difference being time

and scale. At least 50% of the total volume of whole and fragmented kidney stones has naturally undergone repeated events of in vivo dissolution and recrystallization (Sivaguru et al., 2021). The risk of kidney stone presentations increases after hot days, likely due to greater insensible water losses resulting in more concentrated urine and altered urinary flow. Higher temperatures due to climate change is expected to increase the prevalence of kidney stones (Kaufman et al., 2022).

Poorly crystalline and amorphous precipitate is one of the components of the so-called infectious urinary stones, which are the result of urease-producing microorganisms activity, mainly from *Proteus mirabilis*. The main component of this kind of stones is crystalline struvite ($MgNH4PO4{\cdot}6H2O$). Bacteria can build into the structure of the urinary stone and as a result, they are one of the components of the urinary stone. From these three components (poorly crystalline and amorphous precipitate, struvite and *Proteus mirabilis*) poorly crystalline and amorphous precipitate exhibits the greatest ability to aggregate (Prywer & Torzewska, 2019).

Kidney stone imaging techniques

Nephrolithiasis is among the oldest urological diseases with treatment strategies dating back to ancient times. Despite the huge number of patients affected by stones, conceptual understanding of many aspects of this disease is lacking such as mechanisms of stone formation and retention, clinical relevance of different stone compositions and formation patterns and associated pathological features of the condition. Different new tools are available to help to answer these

questions. New renal endoscopes enable kidney visualization in much higher definition than was previously possible, while micro-CT imaging is the optimal technique for assessment of stone microstructure and mineral composition in a nondestructive fashion. These tools may provide novel insights for stone formation aetiology for new prevention and treatment strategies and effective management of nephrolithiasis (Borofsky et al., 2016).

Treatment of renal calculi is highly dependent on the chemical composition of the stone which is difficult to determine by standard imaging techniques (Scherer et al., 2015). Noncontrast CT is the most accurate imaging modality for kidney stones owing to high sensitivity, specificity, accurate stone sizing, and the ability to evaluate non-stone-related pathologies. Ultrasonography has a lower sensitivity and specificity than CT, but does not expose patients to ionizing radiation and is cheaper than CT. Ultrasonography has many limitations, but similar performance in the emergency department to that of CT for patients with suspected kidney stones was demonstrated. Ultrasonography is the first-line imaging modality for patients <14 years old and pregnant women. Low-dose CT has many of the same advantages of standard CT and reduces radiation exposure but diagnostic accuracy is reduced in obese patients. In the future, improvements in CT, ultrasonography, kidney ureter bladder radiography, and MRI may improve the accuracy of imaging kidney stones (Brisbane et al., 2016).

Computed tomography in suspected urolithiasis gives information about the presence, location and size of stones. Stone size is a key parameter in treatment decision but data on impact of reformatation and measurement strategies is few. Manual CT-based stone size measurements are most accurate using multiplanar image reformatation with a bone window setting, while measurements on axial planes with different slice thicknesses underestimate true stone size (Reimer et al., 2021). Use of flexible ureteroscopy for treating kidney stone patients has increased compared with shockwave lithotripsy and percutaneous nephrolithotomy. Wide variations in use and timing of postoperative imaging and definitions of stone-free rate make accurate assessments of stone clearance after flexible ureteroscopy challenging. CT provides the most accurate way to assess the presence of residual fragments; but, even when retrieval of fragments is employed, the complete stone-free rate might only approach 55–60% (Ghani & Wolf, 2015).

The "ultrasonic ureteral crossing sign" was found to accurately predict the location of ureteral calculi by Xia et al., (2020), to significantly improve the efficiency of ultrasound examination, and provide a useful basis for follow-up treatment.

Comorbidity

Nephrolithiasis, secondary hyperparathyroidism and cardiovascular complications are associated with disturbances in Ca handling (Grzegorzewska et al., 2016). Osteoporotic fracture associated with calcium dysregulation is more common in patients with kidney stones. Kidney stones presence is a significant predictor for osteoporotic

fracture in patients with chronic kidney disease, meaning that it should be a clinical risk factor for osteoporotic fracture (Han et al., 2019).

Diabetes, obesity, hypertension and metabolic syndrome are risk factors for stone formation, which may lead to hypertension, chronic kidney disease and end-stage renal disease. Management of symptomatic kidney stones has evolved from open surgical lithotomy to minimally invasive endourological treatments leading to a reduction in patient morbidity, improved stone-free rates and better quality of life. Prevention of recurrence requires behavioural and nutritional interventions, as well as pharmacological treatments that are specific for the type of stone (Khan et al., 2016).

The presence of urolithiasis has been shown to be associated with an increased risk of bone fracture in men and women, particularly in adolescents. This increased risk of fracture in patients with urolithiasis may have important implications for public health (Arrabal-Polo & Arrabal-Martin, 2015).

Ketogenic diet is increasingly being used in epilepsy management. Potential side effects of this diet are increased risk of renal stones due to hypercalciuria among other causes. It is recommended to initiate prophylactic measures once ketogenic diet is commenced by maximizing fluid intake and urine alkalinization with estimation of urinary calcium/creatinine ratio and renal ultrasound in patients with relevant symptoms (Nassar et al., 2022).

Antihypertensives are widely prescribed and could influence kidney stone risk by altering urinary calcium excretion. Relative to beta-

blockers, thiazide diuretics were associated with a decreased risk of kidney stone formation in adults aged >65 years, whereas calcium channel blockers had a comparable risk of presenting with a kidney stone (Alexander et al., 2017).

Proton pump inhibitors are widely prescribed and sold globally. Although initially intended for time-limited treatment of acute disorders, such as gastric ulcers and esophagitis, proton pump inhibitors are now commonly used for prolonged durations and are considered safe. Recent studies raised concern over relation between proton pump inhibitors usage and acute kidney injury, chronic kidney disease, end-stage renal disease, and electrolyte abnormalities. Survey on over ten million FDA Adverse Event Reporting System records provided evidence of kidney injury and electrolyte imbalances in an alarming number of patients taking proton pump inhibitors (Makunts et al., 2019).

Prevention

Colonization of the intestine with Oxalobacter formigenes is associated with a reduced risk of calcium oxalate kidney stones. Bioactive factors derived from these probiotic bacteria stimulate oxalate secretion in the distal colon, leading to a reduction in urinary oxalate excretion (Carney, 2016).

Diet to prevent the recurrence of idiopathic calcium-containing kidney stones are effective. However, lifelong commitment to prevention is challenging for most of the patients. Providers should prioritize the most important dietary recommendations, reserving those less

important for follow-up, and address any confusion patients have from information received prior to evaluation (Penniston et al., 2016).

Cystinuria is an incompletely dominant disorder characterized by defective urinary cystine reabsorption that results in the formation of cystine-based urinary stones. Current treatment options are limited in their effectiveness at preventing stone recurrence and are often poorly tolerated. Nutritional supplement α-lipoic acid inhibits cystine stone formation in mouse model of cystinuria by increasing the solubility of urinary cystine (Zee et al., 2017).

CONCLUSIONS

The incidence and prevalence of kidney stones was increased during past four decades. The prevalence peaks at 40–60 years. Kidney stone formation pathogenesis has multiple steps including complex interactions between protein matrix and mineral components. A protein group (named as 'stone modulators') in inhibition or promotion of stone formation has critical roles. Component of stones are calcium oxalate, calcium phosphate, infection stone, uric acid stone and cystine. Urinary stone disease has associations with antibiotic-driven shifts in the microbiome. Amount of some elements within human calcium-based urinary stones does not correlate with their normal urinary concentrations. This may be due to accumulation or other processes affecting elemental composition of Stones. Genome-wide associations indicate that several genes and molecular pathways contribute to stone formation risk. There is a need of a standardized stone classification system which may improve study and care of stone formers.

There is a great need for recurrence prevention that requires a better understanding of the mechanisms involved in stone formation to facilitate the development of more-effective drugs.

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CHAPTER 7

NATURE OF PROSTATE & PROSTATIC DISEASES: A REVIEW

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1. INTRODUCTION

Androgen-sensitive organ prostate is a male exocrine gland secreting seminal fluid components. Benign prostatic hyperplasia, prostatitis and prostate cancer are widespread conditions affecting majority of elder males. Glucose-regulated protein 78 has a significant role in the development of benign prostatic hyperplasia. mTOR inhibitors are emerging as potential subtype-specific therapeutic option for benign prostatic hyperplasia. Herbal extracts are available for inhibiting androgen receptor activity and expression. Inflammatory/immune markers, hormone markers and tumor-related proteins are associated with chronic prostatitis. Many studies investigated microRNAs as aggressive prostate cancer prognostic biomarkers.

Here in this review, some information from latest articles published on prostatic diseases are summarised.

The prostate is a male exocrine gland secreting seminal fluid components (Francis & Swain, 2018). It is an androgen-sensitive organ needing proper androgen/androgen receptor signals for normal development. The progression of prostate diseases (benign prostate hyperplasia and prostate cancer) also needs proper androgen/androgen receptor signals (Wen et al., 2015). Environmental and nutritional factors, including fatty acids are associated with prostatitis, benign prostate hyperplasia and prostate cancer. Different fatty acid qualities result with different metabolic phenotypes and impact prostate size, epithelial volume, inflammation and gene expression (Ferrucci et al.,

2019). The high-fat diet stimulates increases in lipids and can be harmful to prostatic morphogenesis (Veras et al., 2021).

Stem and progenitor cells of the adult prostate epithelium were believed to locate mainly within the basal cell compartment and possess basal-like phenotypic characteristics. Evidence of existence of luminal epithelial cells exhibiting stem/progenitor properties was obtained in the last decade by lineage tracing and by functional characterization of sorted luminal-like cells. Single-cell transcriptomics led to increasingly exhaustive profiling of putative mouse luminal progenitor cells and to identification of cognate cells in human prostate. The enrichment of luminal progenitor cells in genetically modified mouse models of prostate inflammation, benign prostate hypertrophy and prostate cancer, and the intrinsic castration tolerance of these cells, suggest their potential role in prostate pathogenesis and in resistance to androgen deprivation therapy (Baures et al., 2022).

Benign prostatic hyperplasia and associated lower urinary tract symptoms are widespread conditions affecting majority of elder males (Gudmundsson et al., 2018).

2. Benign prostatic hyperplasia

Benign prostatic hyperplasia is a significant public health burden due to disease sourced morbidity and many available remedies. As much as 70% of men over 70 develop benign prostatic hyperplasia (Hellwege et al., 2019). Benign prostatic hyperplasia is common noncancerous prostate enlargement usually associated with lower urinary tract symptoms. It may lead to complex urinary, bladder, or kidney diseases.

The majority of elderly men will probably be affected by benign prostatic hyperplasia with increases in ages (Li & Klein, 2021). Human prostate is an androgen-dependent gland and an imbalance in cell proliferation may lead to benign prostatic hyperplasia, which results with voiding lower urinary tract symptoms. Evidences suggest that benign prostatic hyperplasia might represent an element into the wide spectrum of disorders conforming the Metabolic syndrome (Gallardo & Quintar, 2021).

Underlying molecular features of benign prostatic hyperplasia remains poorly understood with limited therapeutic options. mTOR inhibitors are emerging as potential subtype-specific therapeutic option. Men exposed to mTOR inhibitors decrease prostate size significantly (Liu et al., 2020). It was proved that the "Hedgehog" is implied as an effective and fundamental regulatory growth factor signal for organogenesis, homeostasis, and regeneration. "Smoothened", as the major control point of Hedgehog signals, activates aberrantly in most human solid tumors. Smoothened cascade may play significant roles in the development of benign prostatic hyperplasia and might be a promising therapeutic target for benign prostatic hyperplasia (Liu et al., 2021). Induction of myofibroblast phenotype may lead to benign prostatic hyperplasia progression through M2 macrophage-mediated IL4 signalling and IL4 may be a therapeutic target to prevention of M2 macrophage activation and fibroblast-to-myofibroblast differentiation (Sheng et al., 2018). Existing scientific evidences is not completely explaining the pathogenesis of benign prostatic hyperplasia. Glucose-regulated protein 78 is a member of the heat shock protein 70

superfamily. It as an important regulator in diversifed types of diseases. Glucose-regulated protein 78 has a significant role in the development of benign prostatic hyperplasia and it may be a new target for treatment of benign prostatic hyperplasia (Fu et al., 2022).

Male gout is positively related to benign prostatic hyperplasia, particularly in young gout patients and those with gouty nephropathy (Li et al., 2018).

Amazon rainforest tree "Pao Pereira" (*Geissospermum vellosii*) bark extract is a herbal preparation reported as inhibitor of prostate cancer cell proliferation. Pao extract suppresses testosterone-induced benign prostatic hyperplasia development through inhibiting androgen receptor activity and expression. Pao extract may be a safe agent for benign prostatic hyperplasia (Liu et al., 2019). Prostatic hyperplasia is characterized by progressive hyperplasia of glandular and stromal tissues. A high-fat diet is usually a main factor inducing oxidative stress, inflammation and abnormal states of prostate. Mangosteen pericarp powder contain plenty of xanthones which is an antioxidant, anti-inflammatory and antiproliferative agent. Mangosteen pericarp powder supplementation can be used to attenuate the progression of prostatic hyperplasia (Tsai et al., 2020). Metabolic syndrome and obesity are linked with hyperuricemia. It was proposed that oxidative stress associated with hyperuricemia may promote benign prostatic hyperplasia. Antihyperuricemic allopurinol use is associated with lowered risk of benign prostatic hyperplasia medication, diagnosis and

surgery. A possible explanation could be antioxidative effects of urate-lowering allopurinol (Kukko et al., 2018).

Clinical guidelines have conflicting recommendations on prostate artery embolization role which is a novel interventional radiology technique to treat benign prostatic hyperplasia. With the absence of consensus among clinicians, patients may seek information online. Approximately 1/4 of websites and 1/2 of videos contain misinformation, inaccuracy or non-evidence-based claims about prostate artery embolization (Huang et al., 2021). Convective radiofrequency water vapor thermal therapy with the Rezum system is a relatively new treatment for benign prostatic hyperplasia (BPH) as a minimally invasive option for management with moderate improvement in symptoms and flow rate. The results are independent of prostate size or presence of a median lobe (Mollengarden et al., 2018).

3. Prostatitis

Chronic prostatitis is a complex disease. Infection and autoimmunity factors may be associated with chronic prostatitis. Inflammatory/immune markers such as immunoglobulin E, Complement C3, Complement C4, C-reactive protein, anti-streptolysin and rheumatoid factors; hormone markers such as osteocalcin, testosterone, follicle-stimulating hormone, and insülin; tumor-related proteins such as carcinoembryonic and PSA, and a nutrition-related variable (ferritin) were significantly associated with chronic prostatitis or subtypes (Chen et al., 2017).

Chronic prostatitis/chronic pelvic pain syndrome is a common problem with unclear etiology. Some diet and lifestyle factors were thought to correlate with this syndrome. Diet and lifestyle factors are associated with chronic prostatitis/chronic pelvic pain syndrome. These modifiable conditions are potential targets for its treatment (Chen et al., 2016). Chronic Prostatitis/Chronic Pelvic Pain Syndrome is often associated with erectile dysfunction (Alkan et al., 2018). This syndrome is a common syndrome with limited therapies and an unknown etiology. Commensal bacterial isolate *Staphylococcus epidermidis* inhibit the colonization, pain responses, and immunological activation to uropathogenic bacteria, emphasizing the power of a healthy prostatic microflora in controlling health and disease (Murphy et al., 2018). Chronic prostatitis/chronic pelvic pain syndrome is difficult condition to evaluate, as it is without a diagnostic "gold standard". There are diversified promising seminal biomarkers to categorize and monitor therapies in chronic prostatitis/chronic pelvic pain syndrome. Inflammatory seminal biomarkers IL6, IL8, TNFα and IL1β are the frequently studied and most promising candidates (Moryousef et al., 2021). Alpha-blockers and antibiotics are frequently used to treat chronic prostatitis/chronic pelvic pain syndrome. Increasing evidences also suggests acupuncture as an effective strategy. The incidence of adverse events of acupuncture was relatively rare compared to alpha-blockers and antibiotics. Electro-acupuncture/acupuncture may be recommended for the treatment of chronic prostatitis/chronic pelvic pain syndrome (Qin et al., 2016). Currently, there is no efficacious treatment method for chronic prostatitis type IIIb/chronic pelvic pain

syndrome. Low-intensity shockwave therapy is a safe and effective treatment method for chronic prostatitis type IIIb/chronic pelvic pain syndrome which improve pain and quality of life. Lack of any side-effects, and the potential for repetition make low-intensity shockwave therapy a promising treatment choice for chronic prostatitis type IIIb/chronic pelvic pain syndrome patients (Mykoniatis et al., 2021).

New data show that Zika virus causes acute and chronic prostatitis in mice and macaques. These observations have implications for the potential long-term health effects of Zika virus infection in men (Stone, 2019). Mental health disorders in chronic prostatitis/chronic pelvic pain syndrome have been widely studied. prostate-derived cytokines, especially IL-1β, cross the blood brain barrier and may lead to enhanced ERK1/2 signaling in several brain areas, possibly underlying induction of chronic prostatitis/chronic pelvic pain syndrome-related mental health disorders (Hu et al., 2016).

Epidemiologic studies suggest that history of prostatitis increase prostate cancer risk but histological prostate inflammation decreases risk. The relationship between a clinical history of prostatitis, histologic inflammation and prostate cancer risk relationship is uncertain. Benign prostate specimens, race, and histological inflammation were important cofactors in the relationship between clinical prostatitis and prostate cancer. Clinical prostatitis was associated with a slightly decreased risk for prostate cancer in African American men. In white men, the relationship between clinical prostatitis and prostate cancer risk was modified by histological prostatic inflammation, Prostate Specific

Antigen velocity, and frequency of Prostate Specific Antigen testing—suggesting a complex interplay between these indications of prostatic inflammation and prostate cancer detection (Rybicki et al., 2016).

4. Prostate cancer

Prostate cancer is the second most common cancer globally in men, and in some countries is the most diagnosed form of cancer now. It is necessary to differentiate benign and malignant prostate for accurate diagnoses. Mueller matrix mapping of the depolarisation distribution of prostate tumour tissues can accurately differentiate between adenoma and carcinoma, and between different grades of carcinoma (Ushenko et al., 2021). Prostate cancer incidence is much lower in Asian men than in Western men. Prostate cancer has strong association with prostatitis and benign prostatic hyperplasia. Prostatitis interacts with benign prostatic hyperplasia, result with higher relative risk of prostate cancer in patients suffering from both conditions (Hung et al., 2013).

Benign prostatic hyperplasia and prostate cancer are two common disorders affecting prostate. Both have an increased incidence with advance in age. Ageing and cellular damages such as infection, toxins, chemical injury or physical injury result with cellular senescence and senescent cell accumulation in tissues. Senescent cells are unable to replicate but are metabolically active and secrete inflammatory mediators, known as the senescence-associated secretory phenotype. Senescent cells are detected via using senescence markers in nearly all human samples of benign prostatic hyperplasia. Roles of many components of the senescence-associated secretory phenotype has been

established in benign prostatic hyperplasia initiation and progression. The role of cellular senescence in prostate cancer is less clearly established. Senescence may act mainly by influencing the senescent stroma on adjacent epithelial cells, favouring cancer initiation, progression and metastasis. Demonstrating the role of senescence in these two age-related prostatic diseases presents new therapeutic opportunities with treatments aiming to remove senescent cells (senolytics) and/or to target components of the senescence-associated secretory phenotype (senescence-associated secretory phenotype inhibitors or senomorphics) (Fiard et al., 2021).

One of the most important but less understood step of epithelial tumourigenesis occurs when cells acquire the ability to leave their epithelial compartment. This phenomenon, described as basal epithelial cell extrusion (basal extrusion), represents the first step of tumour invasion (Rambur et al., 2020).

Magnetic resonance imaging (MRI) provides detailed anatomical images of the prostate and its zones. It has a crucial role for many diagnostic applications. Automatic segmentation such as that of the prostate and prostate zones from magnetic resonance images facilitates many diagnostic and therapeutic applications. However, the lack of a clear prostate boundary, prostate tissue heterogeneity, and the wide interindividual variety of prostate shapes make this a very challenging task (Aldoj et al., 2020). Combined magnetic resonance imaging/Ultrasound fusion targeted biopsy (TBx) and systematic biopsy results in better prostate cancer detection relative to either TBx

or systematic biopsy alone, while at the cost of higher number of biopsy cores and greater detection of clinically insignificant PCa (Hou et al., 2022). Multiparametric magnetic resonance imaging targeted biopsy has been shown to identify more clinically-significant cancers and reduce the detection of clinically-insignificant disease when compared to systematic biopsy; however, the wide-spread accessibility of multiparametric magnetic resonance imaging is limited. A potential strategy for reducing the cost, study time, and contrast-associated risks associated with multiparametric magnetic resonance imaging is elimination of the dynamic contrast-enhanced sequence, relying instead on biparametric magnetic resonance imaging. biparametric magnetic resonance imaging has been shown to have a diagnostic accuracy and cancer detection rate that are equivalent to those of multiparametric magnetic resonance imaging (Porter et al., 2020). Multiparametric magnetic resonance imaging, the use of three multiple imaging sequences, typically T2-weighted, diffusion weighted (DWI) and dynamic contrast enhanced images, has a high sensitivity and specificity for detecting significant cancer. Current guidance now recommends its use prior to biopsy. However, the impact of dynamic contrast enhanced is currently under debate regarding test accuracy. Biparametric magnetic resonance imaging, using only T2 and DWI has been proposed as a viable alternative. Biparametric magnetic resonance imaging offers comparable test accuracies to multiparametric magnetic resonance imaging in detecting prostate cancer. These data are broadly supportive of the biparametric magnetic resonance imaging approach

but heterogeneity does not allow definitive recommendations to be made (Bass et al., 2021).

18F-Fluciclovine PET/CT shows good performance in patients with recurrent prostate cancer leading to measurable clinical benefits (Rais-Bahrami et al., 2021).

Targeted radionuclide therapy with Actinium-225-labeled prostate-specific membrane antigen ligands (225Ac-PSMA) has emerged as a promising treatment modality in the management of metastatic castration-resistant prostate cancer (mCRPC). With its high linear energy transfer and short path length, 225Ac induces double-stranded DNA breaks and is expected to have excellent efficacy and safety profile. 225Ac-PSMA RLT is an efficacious and safe treatment option for patients with mCRPC (Satapathy et al., 2021).

Although overall adiposity should be cautiously interpreted in regards to survival, high muscle mass and subcutaneous adipose tissue, and low "visceral adipose tissue"/"subcutaneous adipose tissue" ratio values are associated with overall survival in men with prostate cancer (Lopez et al., 2021).

Reliable prognostic biomarkers to distinguish indolent from aggressive prostate cancer (PCa) are lacking. Many studies investigated microRNAs (miRs) as PCa prognostic biomarkers, often reporting inconsistent findings. Systematic review identified 120 miRs as prognostic. Five (let-7b-5p, miR-145-5p, miR152-3p, miR-195-5p, miR-224-5p) were consistently associated with progression in multiple cohorts/studies. In the reanalysis, ten (let-7a-5p, miR-148a-3p, miR-

203a-3p, miR-26b-5p, miR30a-3p, miR-30c-5p, miR-30e-3p, miR-374a-5p, miR-425-3p, miR-582-5p) were significantly prognostic of biochemical recurrence (Rana et al., 2022). BRCA1 and BRCA2 pathogenic variants are associated with prostate cancer (PCa) risk. Risks may be modified by age and ethnicity, and for BRCA2 carriers by pathogenic variants location within the gene (Nyberg et al., 2021).

A great number of DNA-damage repair pathways have been recognized to be frequently dysregulated in advanced stages of prostate cancer. DNA-repair defects in prostate cancer represents a clinically relevant disease subset. Tumors whose ability to repair double-strand DNA breaks by homologous recombination is compromised, are highly sensitive to blockade of the repair of DNA single-strand breaks via the inhibition of the enzyme poly(ADP) ribose polymerase (PARP). Olaparib has been the first agent showing a benefit in terms of rPFS and ORR alone or in combination with abiraterone plus prednisone in patients with DNA-damage repair deficiency prostate cancer. Also rucaparib showed a benefit in terms of PSA response rate and ORR in patients with BRCA2 and BRCA1 mutation in a phase-II study. Other phase-III clinical trials are evaluating niraparib and talazoparib, alone or in combination with AR signaling inhibitors (Ratta et al., 2020). Wenzel et al., (2021) performed a systematic review and network meta-analysis focusing on overall survival and adverse event according to the most recent apalutamide, enzalutamide, and darolutamide reports. The meta-analysis suggested the highest overall survival efficacy and lowest grade 3+ toxicity for darolutamide. However, in the PSA-DT ≤ 6 months subgroup, the highest efficacy was recorded for enzalutamide.

The increasing incidence and declining mortality rates seen in prostate cancer will result in a growing survivorship with a burden of health conditions, warranting attention to psychological health. Depression, anxiety, and distress have prognostic significance; attempts have been made to reduce them with psychological interventions using cognitive- and/or education-based approaches (Mundle et al., 2021).

5. Conclusions

Glucose-regulated protein 78 has a significant role in the development of benign prostatic hyperplasia. mTOR inhibitors are emerging as potential subtype-specific therapeutic option for benign prostatic hyperplasia. Herbal extracts are available for inhibiting androgen receptor activity and expression. Inflammatory/immune markers, hormone markers and tumor-related proteins are associated with chronic prostatitis. Many studies investigated microRNAs as aggressive prostate cancer prognostic biomarkers. Targeted radionuclide therapy with Actinium-225-labeled prostate-specific membrane antigen ligands has emerged as a promising treatment modality in the management of metastatic castration-resistant prostate cancer.

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CHAPTER 8

NON-NEOPLASTIC SURGICAL DISEASES OF THE DUODENUM

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INTRODUCTION

The duodenum is the widest and shortest part of the small intestine, measuring 25-30 cm between the pyloric sphincter of the stomach proximally and the jejunum distally. The content, which passes from the stomach to the duodenum through the pyloric sphincter in a controlled manner, is digested here by enzymes originating from the gallbladder, liver and pancreas. Hypertrophic pyloric stenosis, duodenal atresia and superior mesenteric artery syndrome are the most common congenital anomalies that require surgical treatment. Duodenal perforation (DP) is a rare but life-threatening injury. Although there are many etiological factors such as peptic ulcer disease (PUD), iatrogenic causes and trauma in the development of DP, it is reported in the literature that the mortality rate in DP is 8-25%. Although significant advances have been made in endoscopic interventions in the treatment of DPs, surgical procedures are still the most common form of treatment. In this section, the anatomy and histology of the duodenum will be briefly reviewed. Clinical presentations, diagnostic methods, endoscopic and surgical treatment methods of common congenital diseases that require surgical treatment, traumatic and iatrogenic injuries will be presented.

1. ANATOMY AND HISTOLOGY OF THE DUODENUM

The duodenum is located in the continuation of the pyloric region of the stomach and forms the first part of the small intestine. The duodenum,

which is the widest and shortest part of the small intestine, is 25-30 cm long and continues distally as the jejunum.

The duodenum consists of four segments:

1. The duodenal ampulla is attached to the lower surface of the liver via the hepatoduodenal ligament. This ligament includes the portal vein, hepatic artery, and common bile duct.
2. The descending segment is just above the right kidney and inferior vena cava, and surrounds the head of the pancreas in a C shape.
3. The third segment runs from the right to left in front of the aorta and inferior vena cava. In front of this segment are the superior mesenteric vessels.
4. The fourth segment is the last segment of the duodenum and continues as the jejunum.

The wall of the duodenum consists of the mucosa, submucosa, muscularis propria, and serosa from the inside out. The innermost mucosal layer comprises the simple columnar epithelium containing microvilli and numerous mucus glands. The submucosal layer is rich in connective tissue, and the vessels and nerves of the intestine are located in this layer. The muscular layer consists of smooth muscles. These smooth muscles facilitate forward peristaltic movement and mixing of chyme. The serosal layer is characterized by the squamous epithelium and acts as an external barrier between the duodenum and other organs (Shaikh et al., 2022; Soriano et al., 2022).

Content that passes from the stomach to the duodenum through the pyloric sphincter in a controlled manner is digested here by enzymes. These enzymes originate from the gallbladder, liver and pancreas and are taken into the duodenum by the major and minor papillae in the descending segment. The duodenal papilla is surrounded by the sphincter of Oddi, which is the muscle that prevents the backflow of the contents of the duodenal lumen into the bile and pancreatic ducts (Collins et al., 2022; Hundt et al., 2022).

When the pH of the content in the duodenal lumen falls below a certain level, neutralization is achieved through the stimulation of water and bicarbonate secretion by the secretin released from the duodenal epithelium. As a result of this process, pancreatic amylase and lipase function optimally, aiding digestion. Cholecystokinin, another hormone secreted from the duodenal epithelium, helps digestion by providing the flow of accumulated bile into the duodenum through the contraction of the gallbladder.

During the embryological process, the duodenum develops from the most caudal part of the foregut. However, as the stomach expands to the left and is held partially fixed by the enlarged liver and pancreas, the duodenum does not undergo any rotation and instead assumes its classical C-shaped appearance. Due to this process, the distal part of the duodenum is located below the superior mesenteric artery (SMA). During embryological development, the peritoneal layer of the duodenum fuses with the peritoneal layers lining the abdominal cavity and becomes a secondary retroperitoneal organ.

The proximal segment of the duodenum is supplied by the branches of the gastroduodenal and superior pancreaticoduodenal arteries. The distal segment of the duodenum is supplied by SMA and the inferior pancreaticoduodenal artery. Venous drainage runs parallel to the arteries and eventually drains into the liver via the portal vein. The lymphatics of the duodenum drain into the pancreaticoduodenal lymph nodes located along the pancreaticoduodenal vessels and superior mesenteric lymph nodes.

The parasympathetic innervation of the duodenum is mediated by a rich neural network that includes the branches of the anterior and posterior vagus trunks. These nerves pass through the celiac plexuses and extend toward the duodenum, and then synapse in the ganglia in the intestinal plexuses of the duodenum and reach their destination via short postsynaptic fibers.

Sympathetic innervation originates from the branches of the celiac plexus stretching from T5 to T9. These nerves pass through the sympathetic chain along the greater splanchnic nerves in the celiac ganglia. The postsynaptic sympathetic nerve extends from the branches of the celiac trunk to the duodenum. The branches of the autonomic nervous system entering from the duodenum wall innervate the organ by making a plexus along the submucosal layer in the wall.

The muscular layer of the duodenum contains circular and longitudinal muscles. Peristalsis occurs with the contraction of these muscles extending along the entire gastrointestinal tract.

Duodenojejunal flexion is a sudden turn defined by the localization of the inferior mesenteric vein. The duodenojejunal flexure is attached to the posterior abdominal wall by the ligament of Treitz. Except for the first segment, the rest of the duodenum is located retroperitoneally and fixed in the posterior abdominal cavity, and has no mesentery.

The distal end of the common bile duct joins with the pancreatic duct to form the biliopancreatic ampulla, which opens into the major duodenal papilla (papilla of Vater) located in the second segment of the duodenum. This main papilla of the duodenum is important for endoscopic retrograde cholangiopancreatography (ERCP) procedures.

2. NON-NEOPLASTIC SURGICAL DISEASES OF THE DUODENUM

2.1. Congenital Anomalies of the Duodenum

2.1.1. Hypertrophic Pyloric Stenosis (HPS)

HPS, a congenital anomaly, is caused by the hypertrophy of the pyloric sphincter smooth muscle. It is seen in 0.5-1% of infants. The clinical presentation is a gush of non-bilious vomit shortly after feeding. Since obstruction occurs before the duodenal papilla enters the duodenal cavity, the vomit itself is non-bilious. In physical examination, this hypertrophic sphincter can be felt as an olive-shaped mass or a small node in the epigastric region at the edge of the right rib. The treatment of HPS is usually surgical interventions, including pyloric sphincter myomectomy (El-Gohary et al., 2018).

2.1.2. Duodenal Atresia

Duodenal atresia occurs as a result of the congenital complete closure of the duodenal lumen. Polyhydramnios can be seen during pregnancy, and intestinal obstruction symptoms are present in the newborn. The common radiographic finding is the “double bubble”. The air in the stomach and the first segment of the duodenum, separated by atresia, appear as a double bubble. Duodenal atresia can be associated with Down syndrome. The treatment is surgical interventions, including duodenoduodenostomy (Miscia et al., 2019).

2.1.3. Superior Mesenteric Artery Syndrome (SMAS)

SMAS occurs when the third or fourth segment of the duodenum is compressed by SMA and the abdominal aorta. The clinical presentation is typically nausea, vomiting, abdominal pain, early satiety, and bloating. This compression occurs when retroperitoneal fat or lymph tissue that protects the duodenum from compression is reduced. Congenital causes include an asthenic body structure, different orientation of the duodenum in the ligament of Treitz, or low origin of SMA, while other predisposing factors are retroperitoneal tumors, lumbar lordosis, abdominal trauma, rapid linear growth spurt, and weight loss (Lopez et al., 2022).

2.2. Duodenal Perforation (DP)

DP is a rare but life-threatening injury. Among the causes of DP, there are many etiological factors, such as perforated duodenal ulcer (PDU),

iatrogenic causes, and trauma (Ansari et al., 2019; Lopez et al., 2022). It is reported in the literature that DP has a mortality rate of 8-25% (Lau et al., 2011; Møller et al., 2011).

Helicobacter pylori infection and use of non-steroidal anti-inflammatory drugs (NSAIDs) are the two main causes of PDU and related DP (Behrman, 2005). Although its incidence has decreased in recent years, PDU is still the most common cause of DP (Sung et al., 2009). Smoking, physiological stress, previous PDU history, and use of corticosteroids are risk factors for PDU (Vergara et al., 2005). Although it is known that alcohol consumption increases gastrin secretion and damages the gastric mucosa, clinical studies have not determined alcohol as a cause of PDU (Chung & Shelat, 2017). Other causes of DP include duodenal diverticulum (Thorson et al., 2012), infectious diseases (tuberculosis, rotavirus, norovirus, and *Ascaris lumbricoides*) (Berney et al., 1998; Sarmast et al., 2011; Ueda, 2016), autoimmune conditions including scleroderma, Crohn's disease, and abdominal polyarteritis nodosa (Ebert et al., 1997; Katz et al., 1983; Tun & Malik, 1994), duodenal ischemia (Haruna et al., 2012), gallstones adhered to the duodenal wall (Thomas et al., 1976), chemotherapy (Vaidya et al., 2013), tumors (Negoi et al., 2015), iatrogenic causes (Cirocchi et al., 2017; Machado, 2016), trauma (Pandey et al., 2011), foreign bodies (Kusters et al., 2014), and spontaneous perforation (Nazzal et al., 1996).

Endoscopic methods include various frequently used diagnostic and treatment procedures, and the frequency of DP continues to increase due to the widespread use of these procedures (Cirocchi et al., 2017).

The incidence of perforation is higher in therapeutic procedures than in diagnostic procedures.

During surgery, surgical instruments can cause DP. Thermal burns may occur due to electrocautery use while duodenal perforation can be seen at a rate of 0.015% due to blunt or sharp dissection (Machado, 2016).

Duodenal injuries are usually associated with other organ and vascular injuries and rarely seen in isolation (Pandey et al., 2011). Ingested foreign bodies usually pass through the gastrointestinal tract without complications, and less than 1% develop perforation. There is a correlation between sharp and thin ingested foreign bodies and the increased risk of perforation (Cho et al., 2014; Dalrymple et al., 2017; Gardner et al., 2017; Kusters et al., 2014). Implanted foreign bodies, such as endoprostheses (Kusters et al., 2014) and artificial vascular grafts (Malgor & Labropoulos, 2012; Saratzis et al., 2008) can lead to fistula and abscess formation or vasculo-enteric fistulas. Spontaneous perforations are mostly seen in newborns, and their underlying cause is unknown (Nazzal et al., 1996).

2.2.1.Perforated Peptic Ulcer (PDU)

Although the incidence of PDU has decreased in recent years, it is still the leading cause of DP (Behrman, 2005; Sung et al., 2009). PDU affects four million people across the world each year and has an incidence rate of 1.5 to 3% (Zelickson et al., 2011; Zittel et al., 2000). Perforation develops in approximately 5% of these patients throughout their lives (Vaira et al., 1997). NSAID use and *H. pylori* infection

remain the leading causes of PDU (Sung et al., 2009). NSAIDs reduce prostaglandin secretion by inhibiting the cyclooxygenase-1 enzyme in the gastrointestinal tract and may cause mucosal damage. The use of NSAIDs may increase the risk of damage to the gastroduodenal mucosa in certain patients; e.g., those aged over 65 years who use antiplatelets, corticosteroids, and anticoagulants and those with co morbidities such as heart disease and a history of PDU (Drini, 2017). Studies reveal that among NSAIDs, piroxicam and ketorolac result in the highest mucosal damage (Castellsague et al., 2012). *H. pylori* infection induces gastric metaplasia, stimulates immune response and gastric acid secretion, and weakens the mucosal barrier, causing duodenal damage and subsequent perforation (Hamlet et al., 1999). Studies report that the prevalence of *H. pylori* in patients with PDU varies between 50 and 80% (Gisbert & Pajares, 2003).

The reason for the decrease in the incidence of PDU in recent years has been attributed to the widespread use of proton pump inhibitors (PPIs) and the effect of eradication therapy on *H. pylori* infection (Sung et al., 2009). Despite these advances in treatment, peptic ulcer complications remain an important health problem. This has been associated the increasing use of NSAIDs and the aging population (Lau et al., 2011; Søreide et al., 2014).

Although nocturnal abdominal pain or feeling of hunger is typical in patients with duodenal ulcer, sudden onset of severe pain in the upper abdomen may indicate perforation. When perforation develops, tachycardia, sudden onset of abdominal pain, and abdominal stiffness

are observed as a classical trilogy. This sudden-onset abdominal pain, unlike duodenal ulcer pain, does not fully respond to medical treatment (Lanas & Chan, 2017). Studies report that ulcer perforation occurs more frequently in the morning hours, which can be explained by the circadian rhythm of acid secretion (Søreide et al., 2015). The clinical manifestations of PDU are defined in three stages: The first phase is characterized by tachycardia, epigastric pain, and cold extremities, seen within the first two hours of perforation development. The second phase covers period from the second to12thhours after perforation, when pain becomes generalized and increases with movements. During this phase, duodenal contents leak into the peritoneal space and move along the right paracolic groove, typical symptoms, such as right lower quadrant tenderness and abdominal stiffness begin to appear. The third phase refers to the period 12 hours after perforation develops and is manifested by abdominal bloating, fever, and hypotension (Chung & Shelat, 2017). Patients with retroperitoneal perforation may present with a calmer clinical state without peritoneal symptoms (Ansari et al., 2019). However, diagnosis may be delayed in immunocompromised or elderly patients, as clinical signs may not be detected. Imaging is of great importance for diagnosis and early resuscitation. Appropriate selection and risk assessment of therapeutic alternatives can reduce the risk of morbidity and mortality associated with PDU (Søreide et al., 2015).

The differential diagnosis of PDU includes various conditions; e.g., abdominal aortic aneurysm, acute coronary syndrome, aortic dissection,

pancreatitis, appendicitis, Boerhaave syndrome, cholecystitis, cholelithiasis, diverticulitis, duodenitis, esophagitis, gastroesophageal reflux disease, foreign body ingestion, gastritis, hepatitis, abdominal hernia, mesenteric ischemia volvulus, and pneumonia. Some tests are used to exclude these diagnoses. An increase in serum amylase of less than four times the normal levels can be associated with PDU (Di Saverio et al., 2014). Serum gastrin levels are useful for diagnosing Zollinger-Ellison syndrome in patients with a history of recurrent ulcers (Chung & Shelat, 2017). Leukocytosis and a high C-reactive protein level indicate the presence of inflammation or infection (Fakhry et al., 2003).

In acute upper abdominal pain, an emergency upright chest radiograph (CXR) is the main diagnostic method for duodenal perforation. During this examination, free air is observed under the diaphragm in 75% of the patients, but this finding may not be present in patients presenting in the early period, immediately after the onset of symptoms (Grassi et al., 2004). A normal CXR does not always rule out duodenal perforation; therefore, it is essential to further evaluate stable patients with clinically suspected duodenal perforation and normal CXR using computed tomography (CT) (Ansari et al., 2019). In patients with acute kidney injury, a non-contrast CT scan is sufficient to detect free air immediately below the anterior abdominal wall, and the diagnostic accuracy of CT in PDU detection is approximately 98% (Kim et al., 2014). Oral diatrizoate may aid in the diagnosis of PDU when a CT scan is not available and upright CXR does not show free air, but the absence

of leakage does not exclude PDU since perforation may close spontaneously (Donovan et al., 1998). Dual-contrast CT is the most valuable method for diagnosing duodenal perforation and shows duodenal wall thickening, extravasated oral contrast, presence of extraluminal air, and periduodenal fluid collection in patients with perforation (Kim et al., 2009). Although CT with an intravenous and oral contrast injection is a valuable imaging technique in detecting duodenal perforation, surgical exploration may be required for diagnosis in some cases (Ansari et al., 2019; Lopez et al., 2022).

Delayed diagnosis in perforation causes a decrease in survival. The optimal method for the treatment of duodenal perforation, especially non-surgical management remains controversial. In addition, the type of repair and the role of the open or laparoscopic technique and gastric diversion procedures in patients requiring surgery have not yet been fully determined. The treatment of duodenal perforation includes conservative, endoscopic and surgical strategies (Figure 1). The main goals of treatment are resuscitation, infection control, nutritional support, and maintenance of gastrointestinal health.

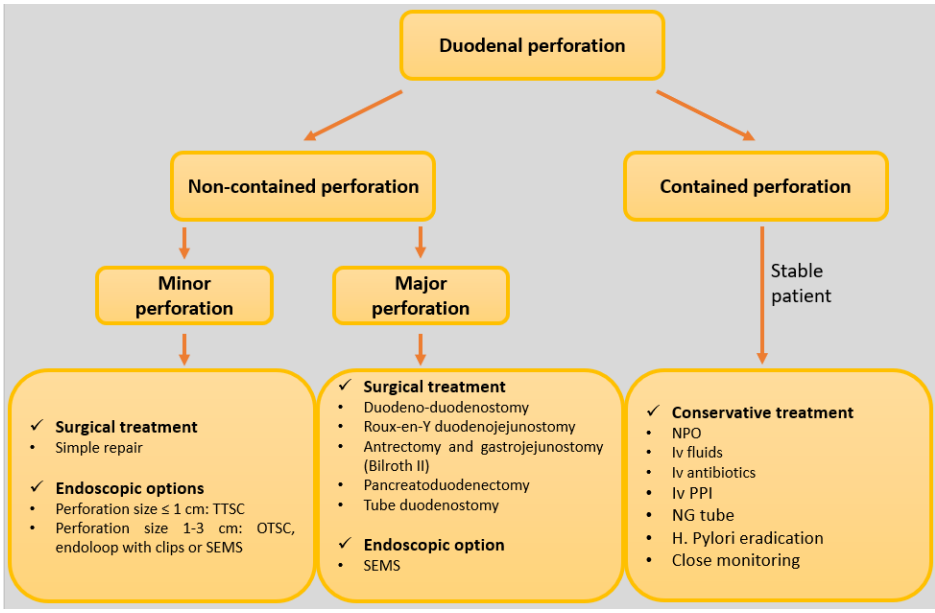

Figure 1: Management algorithm for duodenal perforation

The successful surgical closure of PDU was first reported by Dean in 1894. Today, most duodenal perforations are repaired using the omental patch, a technique first described by Cellan-Jones in 1929 and later modified by Graham in 1937 (Graham, 1937). The first laparoscopic repair of PDU was described in 1990 (Mouret et al., 1990). The management of duodenal perforations depends on the type of perforation, and patients are evaluated in two subgroups as those with limited or free perforation.

Limited perforation: This refers to the closure of the perforated area by the organs adjacent to the duodenum, such as the pancreatic wall, which prevents leakage of free fluid into the peritoneal space. In the literature, it is reported that it is possible to perform conservative treatment in such perforation cases, and the mortality rate is 3% with

conservative treatment and 6.2% with surgical treatment in patients with controlled perforation (Berne & Donovan, 1989). Approximately 50-70% of patients with PDU can be followed up with conservative treatment without the need for surgery (Crofts et al., 1989; Songne et al., 2004). For patients undergoing conservative treatment, gastroduodenography may be performed immediately after admission to investigate contrast medium extravasation. If there is no extravasation in gastroduodenography, conservative treatment can be considered safe (Berne & Donovan, 1989). Conservative management consists of intravenous fluid therapy, nilperos, intravenous PPIs, broad-spectrum antibiotics, eradication of *H. pylori*, and repeated clinical evaluations (El-Gohary et al., 2018). Blood cultures should be taken before starting antibiotics (Gu et al., 2014). Arterial blood gas analysis is valuable in showing metabolic status in septic patients (Søreide et al., 2015).In the literature, it has been reported that somatostatin may be beneficial in the case of a possible enterocutaneous fistula (Rahbour et al., 2012). If there is contrast agent extravasation into the peritoneal cavity, surgical procedures should be considered first, but in high-risk patients who cannot tolerate surgical treatment, the percutaneous drainage of fluid collections may be preferred as a conservative treatment option (Saber et al., 2012).

Free perforation: This is defined as the free leakage of intestinal contents into the abdominal cavity. Minor and major perforations are two subtypes of this group (Ansari et al., 2019).

Minor free perforation: There are two main management strategies for this group: endoscopic approach and surgical repair. Endoscopic treatment is an attractive treatment method because it is minimally invasive and technically easier, and it is recommended to be applied in the early period when inflammatory changes are less obvious (Paspatis et al., 2014). Endoscopic management includes the through-the-scope clip (TTSC), over-the-scope clip (OTSC), clip-on detachable snare ring, and self-expanding metal stent (SEMS) (Ansari et al., 2019). TTSC is suitable for linear perforations smaller than 1 cm, while OTSC, clip-on detachable snare ring, and SEMS are used in cases of 1-3 cm perforation (Paspatis et al., 2014). OTSC can compress larger amounts of tissue than TTSC and is shaped like a bear trap to allow for the full-thickness closure of the tissue (Wei et al., 2019). If the OTSC technique is not available, a combined technique of TTSC and endoloop can be applied (Nakagawa et al., 2010). SEMS is another endoscopic treatment option that can also be a permanent solution for duodenal perforation (Bergström et al., 2013; Jung, 2017; Paspatis et al., 2014). SEMS is another endoscopic treatment option that can be applied to stay permanent for duodenal perforation (Bergström et al., 2013; Jung, 2017).

The choice of surgical treatment depends on the size and localization of perforation, the viability of the duodenal walls, the degree of local contamination, and the underlying etiology.

In simple surgical treatment, the surgeon can repair perforation with or without an omental patch. A free omental plug (Graham patch) can be

used or a pedicled omental flap can be sutured to the perforation using a technique known as Cellan-Jones repair (Ansari et al., 2019; Cellan-Jones, 1929). In addition, the modified Graham technique involves the primary suturing of the perforation area, followed by omentopexy using an omental flap with a pedicle. Apart from these, gelatin sponge and fibrin glue have been developed as sutureless techniques to close perforation. In previous studies comparing primary closure, omentopexy, and segmentation (without closure), no significant difference was observed in postoperative morbidity and mortality rates (Abd Ellatif et al., 2013; Lau et al., 1996; Lin et al., 2017). Surgical repair can be performed with conventional open surgery or laparoscopy. The results of a recent meta-analysis including seven randomized controlled trials showed that the laparoscopic approach in the treatment of PDU provided significant advantages in terms of postoperative complications and length of hospital stay (Quah et al., 2019). The routine placement of abdominal drains after surgical repair is controversial, and according to the literature, it has no benefit in preventing postoperative fluid collection or abscesses. In addition, drains may be associated with increased morbidity, such as drain wound infection (Pai et al., 1999).

Major perforation: This usually requires the use of reconstructive surgery techniques, including duodenoduodenostomy (first choice), Roux-en-Y duodenojejunostomy (second choice), and Billroth II operation (Malhotra et al., 2015). It is recommended that perforations in the first or proximal second segment be managed by performing a

Billroth II operation (Cogbill et al., 1990). Duodenoduodenostomy may be necessary in large duodenal perforations (Malhotra et al., 2015). If this is not possible, Roux-en-Y duodenojejunostomy may be performed. A Billroth II operation may be necessary if the perforation is in the first or proximal second segment of the duodenum. If the duodenopancreatic complex is destroyed, pancreaticoduodenectomy may be required (Cogbill et al., 1990).

Pyloric exclusion includes the surgical repair of the duodenum, gastrostomy, internal closure of the pylorus, and a gastrojejunostomy. However, in recent years, the added benefit of using a gastric diversion procedure, such as pyloric exclusion in duodenal perforation has been questioned. More importantly, this procedure has been associated with more postoperative complications and longer hospital stay compared to simple repair without pyloric exclusion (Cogbill et al., 1990; Cruvinel Neto et al., 2014; DuBose et al., 2008).

Tube duodenostomy is a procedure that can be applied for damage control in large duodenal perforations in cases of extensive duodenal damage, hemodynamic instability of the patient, lack of surgical adequacy for complex reconstruction, and unavailability of other repair techniques (Kutlu et al., 2013).

The main prognostic factor in duodenal perforation is still the time between perforation and treatment, and mortality increases significantly when this interval is more than 24 hours (Cirocchi et al., 2017; Lau et al., 2011; Møller et al., 2010). Other prognostic factors are associated

with the clinical manifestations of sepsis, such as an increased APACHE II score. Advanced age and comorbidities are strong negative prognostic factors (Lee et al., 2001; Møller et al., 2010).

Duodenal perforation can cause acute pain associated with free perforation and non-acute symptoms, such as abscess or fistula formation. Sepsis is common in patients with perforation and is responsible for 40-50% of deaths. Approximately 30-35% of patients have sepsis at the time they reach the operating room, and septic shock develops in more than 25% of patients in the first month of surgery and causes a death rate of 50-60% (Søreide et al., 2015). Postoperative complications develop in 30% of patients, with an age over 40 years, history of septic shock, and large perforation size being reported as risk factors increasing the rate of postoperative complications (Lee et al., 2001). Common surgical complications include pneumonia, wound dehiscence, peritonitis, incisional hernia, enterocutaneous fistula, intra-abdominal abscess, surgical site infection, and ileus. Among these complications, the most common is reported to be surgical site infection seen at a rate of 32% (Sharma et al., 2006).

Prognosis: The mortality rate in patients who develop PDU is reported to vary between 1.3 and 20% (Boey et al., 1987; Hermansson et al., 1999; Rajesh et al., 2003). The postoperative mortality rate in patients with PDU is estimated to be 6-10% (Imhof et al., 2008). In the literature, there are studies reporting that the 30-day mortality rate can reach 20% (Søreide et al., 2014). The American Society of Anesthesiologists (ASA) score and Boey score are the most widely validated scoring

systems used to predict outcomes in duodenal perforation (Chung & Shelat, 2017). The Boey scoring factors include concomitant serious medical illness, preoperative shock, and perforation-treatment time interval being over 24 hours. When all these factors are positive, the total score is 3, which predicts mortality at a rate of 38% and morbidity at 77%. The ASA score uses existing systemic disease and degree of comorbidity as parameters to predict PDU outcome (Thorsen et al., 2013). Important risk factors that increase mortality are comorbidities, resection surgery, presence of septic shock at admission, female gender, elderly patients, metabolic acidosis, delay in treatment for more than 24 hours, acute renal failure, hypoalbuminemia, smoking, and asthenia (Kocer et al., 2007; Noguiera et al., 2003). Studies show that patients older than 65 years have a higher mortality rate than younger patients (Kocer et al., 2007). Delays in treatment for more than 24 hours, being over 60 years old, concomitant diseases, and systolic blood pressure below 100 mmHg are the main risk factors that increase mortality (Sarosi et al., 2005).

2.2.2. Traumatic Duodenum Perforation

Only 20% of duodenal injuries are due to blunt trauma, with the rest being caused by penetrating trauma. While duodenal traumas account for 4.3% of all abdominal injuries, less than 2% of traumatic abdominal injuries involve the duodenum (Watts & Fakhry, 2003). The male:female ratio is 5:1, and 70% of all duodenal injuries are seen in individuals aged 16-30 years. The reason why duodenal trauma presents with a severe clinical state is difficulties in early diagnosis due to most

of the duodenum being located retroperitoneally. This delay in diagnosis results in higher morbidity and mortality rates (García Santos et al., 2015; Malhotra et al., 2015; Tejerina Alvarez et al., 2004).

Gastrointestinal injuries are rarely seen in blunt abdominal traumas, with the incidence rates of bowel, stomach and duodenum injuries after these traumas being reported as 0.81–3.1%, 0.1%, and 0.4%, respectively (Hughes et al., 2002; Tejerina Alvarez et al., 2004; Watts & Fakhry, 2003). One of the mechanisms underlying the initiation of this type of injury is the compression of a hollow internal organ against a hard part of the human body (e.g., the spine and rib cage) due to an external force (such as a force exerted by the seat belt, handlebar, or steering wheel). Another mechanism is the tension that arises between the fixed and moving parts of the hollow internal organ due to sudden deceleration during vehicle braking (Asensio et al., 1993; Coccolini et al., 2019; García Santos et al., 2015; Moore et al., 2017).

Due to its proximity to various organs and structures, such as the right kidney, liver, common bile duct, and colon, injuries to the duodenum rarely occur alone. In duodenal injuries, the most frequently injured organs are the liver (17%) and colon (13%). Anatomically, the most affected area of the duodenum is the second segment (36%), followed by the third (18%), fourth (15%) and first (13%) segments (93.95).

According to the Eastern Association for the Surgery of Trauma (EAST) Hollow Viscus Injury Study, in hollow visceral injuries, the small intestine is the most frequently injured organ, followed by the

colon, duodenum, stomach, and appendix (Asensio et al., 1993; Chen & Yang, 2011; García Santos et al., 2015; Moore et al., 2017). As a result of duodenal trauma, hematoma, laceration and devascularization occur. These cases may present with clinical signs and symptoms, such as vomiting (especially hematemesis) and epigastric pain. Pain that aggravates due to peritoneal irritation and radiates to the waist is a specific finding of duodenal injuries. Other less common clinical presentations are upper quadrant abdominal distension associated with back pain, peritonitis, fever, tachycardia and infrequent borborygmus, and silent guts. In addition, anterior sacral crepitus may be seen on rectal digital examination due to pneumoretroperitoneum. Butler et al. described testicular pain and priapism associated with duodenal injury, possibly due to the stimulation of sympathetic fibers along the gonadal vessels (Bhattacharjee et al., 2011; Chen & Yang, 2011; Fraga et al., 2008; García Santos et al., 2015; Pandey et al., 2011).

In hemodynamically stable patients, the best examination method to evaluate duodenal injury is a CT scan using intravenous and oral contrast material. While this examination shows 86% sensitivity and 88% specificity in diagnosing blunt injury, physical examination has 53% sensitivity and 69% specificity. CT scan findings associated with duodenal injury are mesenteric hematoma (37%) and free fluid (30%). In duodenal perforation, CT may reveal air (or fluid) leakage collecting in the bursa omentalis. Rarely, air or fluid collected here travels through the foramen of Winslow, and pneumoperitoneum is seen. The presence of extraluminal air has high specificity for bowel perforation. As a rarer

finding, Kunin et al. also described the focal thickening of the duodenal wall, with the presence of gas or fluid in the right anterior pararenal space in duodenal perforation (Asensio et al., 1993; Brofman et al., 2006; García Santos et al., 2015; Joseph et al., 2013; Kunin et al., 1993; Moore et al., 2017).

Laboratory findings in the early stages of duodenal injury provide little help in diagnosis. Although serum amylase level may indicate duodenal damage, its sensitivity and specificity are low; therefore, it should not be used as an indicator for the decision of exploratory laparotomy (García Santos et al., 2015).

The diagnosis of duodenal injury in hemodynamically unstable patients is often made by exploratory laparotomy. In such cases, damage control should always be considered, especially if the patient has acidosis, coagulopathy, or hypothermia (García Santos et al., 2015; Malhotra et al., 2015; Moore et al., 2017). In exploratory laparotomy, findings suggestive of duodenal injury include duodenal subcutaneous emphysema, bile in the duodenal wall, free bile fluid, retroperitoneal hematoma around the duodenum, and right perirenal hematoma (Bhattacharjee et al., 2011; Fraga et al., 2008; García Santos et al., 2015; Malhotra et al., 2015; Moore et al., 2017). The first goal in laparotomy performed for traumatic injury is to stop the bleeding, and the second is to identify gastrointestinal damage. In addition, a retroperitoneal hematoma should suggest injury to the retroperitoneal organs or great vessels.

The retroperitoneum is divided into three zones: Zone 1 represents the central region bounded by the aortic hiatus above, the sacral nose below, and the renal hiluses bilaterally on the sides, and includes the abdominal aorta, inferior vena cava, duodenum, and pancreas (Daly et al., 2008). Explorative laparotomy is mandatory in both penetrating and blunt injuries, since the presence of a retroperitoneal hematoma in zone 1 means injury to the large vessels, duodenum, or pancreas. During exploration, the Kocher maneuver can be performed to examine the first and second segments of the duodenum. After that, right medial visceral rotation (the Cattell-Braasch maneuver) can be undertaken to examine the inferior vena cava, the infrarenal aorta, the third segment of the duodenum, and the head of the pancreas. The omental bursa can be opened to examine the body and tail of the pancreas (Manzini & Madiba, 2014; Petrone et al., 2018).

The American Association for Surgery of Trauma (AAST) Organ Injury Scale classifies duodenal injuries into grades I-V based on the type of lesion (laceration or hematoma), length, and enterovascular effects (Table 1). These categories allow for designing a complete treatment algorithm and help surgeons choose the best approach in each case (García Santos et al., 2015; Malhotra et al., 2015; Moore et al., 2017).

Table 1. Classification of duodenal injuries according to the American Association for Surgery of Trauma Organ Injury Scale (AAST-OIS).

Grade	Injury	Description
I	Hematoma	Involving one portion of duodenum
	Laceration	Partial laceration without perforation
II	Hematoma	Involving more than one portion
	Laceration	Disruption of <50% of circumference
III	Laceration	Disruption of 50-75% of circumference of D2
		Disruption of 50-100% of circumference of D1, D3, and D4
IV	Laceration	Disruption of >75% of circumference of D2
		Involving the ampulla of Vater or distal common bile duct
V	Laceration	Massive disruption of the duodenopancreatic complex
	Vascular	Devascularization of the duodenum

D1 – first portion of the duodenum; D2 – second portion of the duodenum; D3 – third portion of the duodenum; D4 – fourth portion of the duodenum

The management of grade1 hematomas includes nasogastric tube decompression and discontinuation of oral intake. The hematoma may cause duodenal obstruction, and if it persists for more than two weeks, surgical drainage and simple repair should be performed. This intervention is also recommended in the presence of intraoperative evidence of a duodenal hematoma when the lumen is compromised by 50% or more; otherwise, no intervention is necessary. If the hematoma occupies more than 75% of the intestinal lumen, gastrojejunostomy should be performed to prevent delayed duodenal obstruction. Grade I perforation should be primarily repaired (Asensio et al., 1993; Chen & Yang, 2011; Malhotra et al., 2015; Moore et al., 2017).

Grade II hematomas require the same treatment as grade I; however, they can be repaired with simple longitudinal primary tension-free repair immediately after injury, provided that the edges of the laceration site are fresh and clean. Transverse closure is recommended as some

authors suggest that it prevents the narrowing of the intestinal lumen. In cases where tension-free repair is not possible or there is contamination or delay in surgery, a grade II injury should be managed like a grade III injury (Asensio et al., 1993; Chen & Yang, 2011; Malhotra et al., 2015; Moore et al., 2017).

The treatment of grade III injuries can vary. Tension-free repair is recommended whenever possible. In the presence of larger perforations, a part of the organ can be resected and end-to-end duodenostomy can be performed. If duodenal mobilization is not possible due to the lesions in the second segment of the duodenum, Roux-en-Y duodenostomy can be undertaken. If the injury is close to the first or second part of the duodenum, the surgeon may perform antrectomy with gastrojejunostomy (Billroth II procedure) (Asensio et al., 1993; Chen & Yang, 2011; Malhotra et al., 2015; Moore et al., 2017).

If the bile duct and ampulla are intact in grade IV injuries, surgical management can be performed similarly to grade III injuries. Otherwise, grade IV should be treated as grade V (Asensio et al., 1993; Chen & Yang, 2011; Malhotra et al., 2015; Moore et al., 2017).

Grade V injuries have the worst prognosis and usually require damage control surgery. Reconstructive surgery can be performed if the patient survives damage control surgery. Reconstructive surgery may include the replantation of the common bile duct into the duodenum or Roux-en-Y anastomosis. If the duodenum cannot be repaired or the head of

the pancreas is destroyed, pancreaticoduodenectomy (the Whipple procedure) can be undertaken (Asensio et al., 1993; Chen & Yang, 2011; Malhotra et al., 2015; Moore et al., 2017).

Mortality after duodenal trauma can be divided into early (within 48 hours after injury) and late (after 48 hours) mortality, with 75% of all deaths occurring in the early period and usually associated with hemorrhage and central nervous system injuries. Late deaths are mainly due to sepsis, duodenal fistulas, and multiple organ failure. Postoperative complications include abscess development (15%), duodenal fistula formation due to suture line separation (6%), duodenal obstruction (0.9%), and recurrent pancreatitis (0.5%) (Asensio et al., 1993; García Santos et al., 2015; Moore et al., 2017).

According to a study by Santos et al., the mortality rate associated with duodenal trauma ranged from 5.3 to 30% (García Santos et al., 2015). Pancreatic and common bile duct injuries can be counted among the factors that increase the mortality rate. However, the most important factor related to mortality is the delay in diagnosis and surgical repair. According to the lesion classification, the mortality rate is highest in grade IV injuries at 58.8%, while grade I, II and III injuries have mortality rates of 8.3%, 18.7%, and 27.6%, respectively (Asensio et al., 1993; Asensio et al., 2002; Moore et al., 2017).

Octreotide administration for duodenal trauma has two main effects: First, octreotide, as a somatostatin analog, reduces gastrointestinal secretions, including exocrine pancreatic secretions. In this case, the

postoperative administration of octreotide may prevent fistula formation, as well as reducing fluid secretion into the retroperitoneal space. Second, octreotide may also potentially act as a splanchnic vasoconstrictor, helping control possible bleeding in the area. Therefore, octreotide may be an important factor in postoperative recovery after duodenal and pancreatic trauma (Amirata et al., 1994; Ivanov & Grishin, 2004; Ivanov et al., 2003; Lamberts et al., 1996; Mullins et al., 1995).

Complications of duodenal trauma surgery include intra-abdominal abscesses, duodenal obstruction, recurrent pancreatitis, and fistula formation due to suture line separation. Although the mortality rate of duodenal injury varies between 5.3 and 30%, late diagnosis is the most important factor for a higher mortality rate (Asensio et al., 1993; García Santos et al., 2015). It has been reported that duodenal injuries have high morbidity and mortality rates (27.1% and 5.3-30%, respectively), and morbidity is mostly related to intra-abdominal abscesses (15%), followed by duodenal fistulas (6%) (García Santos et al., 2015).

Risk factors for leakage from the duodenal repair site are severe organ damage and the time from injury to repair being greater than 24 hours. It has been reported that these two factors increase morbidity and mortality (Singh et al., 2013). Weale et al. determined that the rate of leakage could increase up to 66% in grade III duodenal injuries treated with primary repair (Weale et al., 2019).

In certain cases, additional procedures should be applied. Duodenal diversion may be considered for poor duodenal repair. There are three types of duodenal diversion: Berne's duodenal diverticulization, pyloric exclusion, and tube duodenostomy. A feeding jejunostomy is a good method to provide early enteral nutrition. Periduodenal drains are not always necessary but should be placed for poor duodenal repair or the duodenal injuries of AAST grade III or higher (Malhotra et al., 2015). An enterocutaneous fistula originating from the upper gastrointestinal tract (close to the duodenojejunal junction) is associated with a higher chance of spontaneous closure (73.3%) than that originating from the lower gastrointestinal tract (35.3%) (Quinn et al., 2017). Approximately 90% of fistula closures occur spontaneously in the first month, while the remaining 10% close in the second month (Gribovskaja-Rupp & Melton, 2016). Nutritional supplements have a positive effects on spontaneous closure. The enteral administration of nutritional supplements is superior to parenteral nutrition. For patients at a high risk of leakage, decompression of digestive juices, access to distal enteral nutrition, and adequate drainage tube placement contribute to treatment.

2.2.3. Perforation due to ERCP

With the widespread use of endoscopic procedures, such as ERCP, iatrogenic duodenal perforation is becoming more common (26). Complications such as pancreatitis, bleeding, and perforation are seen in approximately 10% of patients after ERCP (Wang et al., 2009). The rate of duodenal perforation after ERCP ranges from 0.09 to 1.67%

(Dubecz et al., 2012; Rabie et al., 2013). ERCP perforations may be duodenal due to endoscope trauma, ampullary due to sphincterotomy, or ductal due to instrumentation. The incidence of endoscopic perforation is higher in therapeutic procedures than those performed for diagnostic purposes.

The Stapfer classification classifies post-ERCP perforations into four types. The endoscope itself causes type I perforations (lateral or medial duodenal wall perforations). Type II perforations or peri-Vaterian injuries occur during sphincterotomy. Perforations or distal bile duct injuries caused by basket or wire instrumentation are classified as type III. Type IV perforations are diagnosed based on the presence of retroperitoneal air on imaging and are usually asymptomatic (Stapfer et al., 2000). Stapfer type II perforation is most common after ERCP (58.4%), followed by type I (17.8%), type III (13.2%), and type IV (10.6%) (Cirocchi et al., 2017). Sphincter of Oddi dysfunction, advanced age, anatomical abnormalities, and contrast agent injection are factors that increase the risk of duodenal perforation after ERCP (Enns et al., 2002; Loperfido et al., 1998).

Perforation should be suspected in patients with abdominal pain after ERCP. Diagnosis is made by performing emergency CT of the abdomen, which is very sensitive for extraluminal gas and shows fluid collections well. Oral water-soluble contrast can show whether there is ongoing leakage from the perforation site (Cirocchi et al., 2017).

Non-surgical treatment of ERCP-associated perforation includes the discontinuation of oral intake, nasogastric tube drainage, intravenous antibiotics, and PPIs. The rate of non-operative management is the lowest (13%) in Stapfer type I perforations, moderate (58.1%) in type III lesions, and very high in other types of perforations (84.2% in type II and 84% in type IV). Depending on the patient's condition and the size and location of perforation, parenteral nutrition, percutaneous drainage of the collection with imaging, endoscopic stents, or surgery may be required (Cirocchi et al., 2017).

There are studies showing that early surgical treatment provides favorable outcomes in terms of postoperative mortality and reintervention rates in patients with Stapfer type I perforations. Non-operative treatment should be considered primarily in patients with Stapfer type III and IV perforations. Stapfer II perforations occur when the sphincterotomy extends beyond the wall of the bile or pancreatic duct and their treatment results widely vary. The timing of surgery is very important in these patients, and the postoperative mortality rate is higher in patients who undergo surgery in the late period than those operated in the early period (14.3% vs. 5.9%) (Cirocchi et al., 2017).

Recent advances in the endoscopic treatment of ERCP-associated duodenal perforation are promising. Endoclips, OTSC, SEMS, plastic biliary drainage stents, and endoscopic suture devices can be used in patients diagnosed early (<12 hours) and in centers with advanced equipment and specialists (Park, 2016).

2.2.4. Surgical Injury

Duodenal injury may occur during surgical procedures and may go unnoticed during the operation, presenting as a delayed perforation a few days later as a result of duodenal wall necrosis. Intestinal injuries have been reported to occur in 0.07-0.9% of patients that have undergone laparoscopic cholecystectomy (LC), which is the gold standard in the treatment of benign gallbladder diseases, with 58% of these injuries being detected in the small intestine, 32% in the large intestine, and 7% in the stomach (Agresta et al., 2015; Schrenk et al., 1996; Zafar et al., 2015). In a series of 77,604 patients who underwent LC, the overall incidence of duodenal injuries was reported to be 0.04% (range, 0.01-4%), and the rate of duodenal injury as 0.015% (Deziel et al., 1993; Testini et al., 2008). While the most common LC-related injuries are bile duct injuries, the most serious complications are vascular and intestinal injuries (Bishoff et al., 1999; Deziel et al., 1993; El-Banna et al., 2000; Machado, 2011, 2012; Ress et al., 1993; Zafar et al., 2015). Bowel injury due to LC is usually overlooked during the procedure. The injury is later diagnosed when sepsis, peritonitis, or an intraperitoneal abscess or enterocutaneous fistula develops (Wherry et al., 1996; Wolfe et al., 1991). Injury should be suspected in patients with unexplained postoperative fever, nausea, vomiting, anorexia, and abdominal distention after LC (Croce et al., 1999; Deziel et al., 1993; Testini et al., 2008).

In a large-scale literature review by Machado, the mean time of detection of all injuries in the postoperative period was 1.7 days (0-9 days), and 46% of injuries were detected intraoperatively. In the same study, the cause of injury was found to be cautery in 46% of the cases, dissection in 39%, and traction in 14%. The symptoms and signs of duodenal injuries associated with LC included abdominal pain, nausea, vomiting, abdominal tenderness, defense, fever, peritonitis, bile drainage from the drainage tube, intra-abdominal abscess, sepsis, and septic shock. The injury site was the proximal duodenal papilla in 46% of the cases and the distal duodenal papilla in 15%, corresponding to the second segment of the duodenum in a total of 61% of patients, first segment in 31%, and third segment in 7.6% (Machado, 2016). The authors also noted that 82% of the cases survived. The mean injury detection time was 1.6 days for the survivors and 4.25 days for the patients that died. In particular, 94% of the cases identified on day 1 of injury survived.

In a review of 205,969 cases who underwent laparoscopic procedures, 226 intestinal injuries were identified, of which 50% were caused by cautery and 32% by the Veress needle or trocar insertion (Bishoff et al., 1999). In another study of 329,935 laparoscopic cases, it was determined that 430 intestinal injuries occurred. While 55.8% of these injuries were located in the small intestine, 38.65% were found to be large intestine injuries (van der Voort et al., 2004). Duodenal injuries are likely to be due to thermal damage during cautery use (Bishoff et al., 1999; Testini et al., 2008). Intestinal injury due to cautery has a

higher risk of being overlooked during surgery and may manifest days later as a result of the necrosis of the intestinal wall (Croce et al., 1999; Deziel et al., 1993; Schrenk et al., 1996; van der Voort et al., 2004; Wherry et al., 1996; Wolfe et al., 1991; Z'Graggen et al., 1998).

The average time to detect injuries after LC is reported to be 4.5 days (2-14) for small bowel injuries, 5.4 (1-29) days for large intestine injuries (Bishoff et al., 1999), and 1.7 days (0-5) for duodenal injuries (Testini et al., 2008). The diagnosis of duodenal injury in the postoperative period is often difficult and requires high clinical suspicion due to its rarity (Bishoff et al., 1999; Deziel et al., 1993; Huang et al., 1997; Testini et al., 2008). Pain, which may initially be vague or limited to the right hypochondrium, may later spread to the entire abdomen (Croce et al., 1999; Schrenk et al., 1996)(123, 135). Pain in the early stages can be disregarded since it is a relatively common finding after LC. However, if pain persists for more than 24 hours and increases in intensity, it should raise suspicion (Croce et al., 1999). These patients may have normal liver function test results or show mild elevations of bilirubin and serum amylase with normal alkaline phosphatase levels (Croce et al., 1999; Deziel et al., 1993; Huang et al., 1997; Schrenk et al., 1996). However, in patients with a drain due to difficult cholecystectomy, high amylase levels in the drain fluid can confirm the diagnosis. Amylase level can also be estimated using the ultrasound-guided aspiration of duodenal leak fluid. Imaging with contrast can confirm leakage (Croce et al., 1999). CT scan can detect large fluid accumulation around the duodenum or in the general

peritoneal cavity, depending on when the procedure is performed in the postoperative period (Testini et al., 2008). The presence of more air and fluid in the abdomen than cannot be explained as a postoperative finding and the demonstration of contrast leakage when imaging with oral contrast are consistent with duodenal injury (Croce et al., 1999; Jing & Shuo-Dong, 2014). Air in the region corresponding to the right psoas muscle on direct radiography may indicate retroperitoneal duodenal leakage. When in doubt, at least early diagnostic laparoscopy is recommended, as time is crucial for a better outcome (Croce et al., 1999; Deziel et al., 1993; Testini et al., 2008). The appearance of bile during re-exploration suggests duodenal injury when no leakage from the hepatic bed, cystic duct, or common bile duct is confirmed. Unfortunately, diagnostic laparoscopy fails to detect small perforations, and this misdiagnosis may lead to intra-abdominal or retroperitoneal collection and sepsis in the lumbar region, resulting in a prolonged postoperative period (Croce et al., 1999)(135). If the injury is not apparent during laparoscopy, it may be helpful to perform upper gastrointestinal endoscopy to demonstrate air leakage around the duodenum by blowing air or using methylene blue.

Morbidities seen in duodenal injuries include septicemia, necrotizing fasciitis, pneumonia, incisional hernia, lumbar abscess, and intra-abdominal complications, such as abscess and peritonitis (Croce et al., 1999; El-Banna et al., 2000; Schrenk et al., 1996; Testini et al., 2008; van der Voort et al., 2004). During reoperation for cholecystectomy or

duodenal repair, posterior lumbar abscesses may occur due to the disruption of the posterior peritoneal membrane (Croce et al., 1999).

The treatment of duodenal perforation may require meticulous exploration by intraoperative upper gastrointestinal endoscopy or duodenal mobilization with the Kocher maneuver (Croce et al., 1999). When duodenal injury is detected intraoperatively or by re-exploration shortly after LC, direct repair with an omental patch is possible (Testini et al., 2008), which can be performed laparoscopically when the duodenum is relatively healthy and the perforation area is small (Croce et al., 1999; Kum et al., 1996; Kwon et al., 2001).

In cases of suspected iatrogenic perforation, emergency surgery is recommended to evaluate the abdomen and provide a safe repair (El-Banna et al., 2000; Ress et al., 1993; Testini et al., 2008). However, a more than 48-hour delay in diagnosis may result in duodenal fistula formation by causing an edematous macerated duodenum that cannot retain repair sutures (Bishoff et al., 1999; Deziel et al., 1993; Huang et al., 1997; Singh et al., 2004). Duodenal injury site is a critical factor affecting both the outcome and treatment approach (Bishoff et al., 1999; El-Banna et al., 2000; Schrenk et al., 1996; Testini et al., 2008). Common approaches for injuries immediately above or below the duodenal ampulla include duodenal drainage with a decompression tube, temporary pyloric exclusion, gastrojejunostomy, feeding jejunostomy, external duodenal drainage with a Foley or Petzer tube, and gastric resection (Testini et al., 2008). However, there are conflicting results concerning the superiority of these techniques over

each other (Carrillo et al., 1996; Ivatury et al., 1985). In the presence of large defects and a sensitive duodenal wall, a more aggressive approach, including duodenojejunostomy or duodenopancreatectomy may be adopted (Carrillo et al., 1996; Peters et al., 1991; Testini et al., 2008).

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CHAPTER 9

VAGINOPLASTY SURGERY IN MULLERIAN ANOMALY

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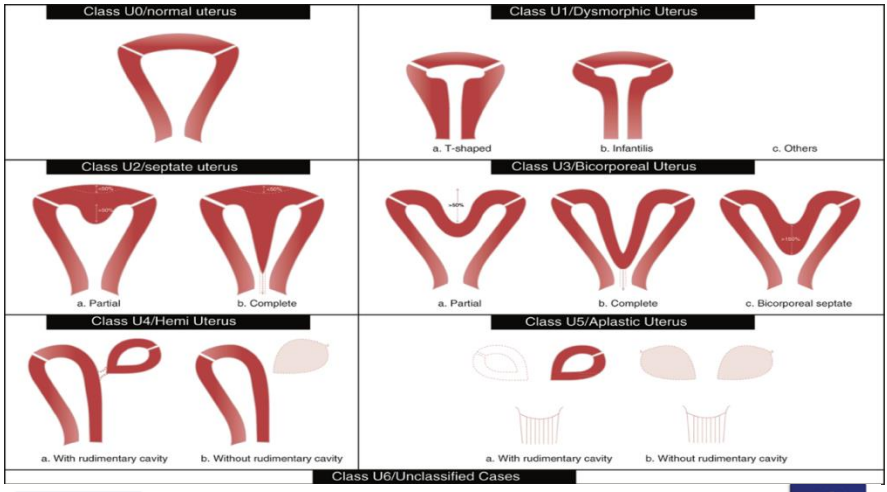
INTRODUCTION

The female reproductive tract develops from a pair of Müllerian ducts that form the structures of the fallopian tubes, uterus, cervix and upper two-thirds of the vagina. The three phases of development include organogenesis, fusion, and resorption of the septum. Failure in one or more of these developmental phases will result in anatomical structural abnormalities in the related organs (Chandler, *et al*., 2009).

Müllerian anomaly is a Müllerian duct malformation that has occurred since the embryonic period. In this condition, early diagnosis is very important because it can reduce the risk of worsening complaints or complications that may occur. Establishing the correct diagnosis will lead to more appropriate patient management both non-surgically and surgically. The most common cause of congenital abnormalities of the female genitalia is Mayer Rokitansky Kuster Hauser syndrome (MRKH), as well as vaginal agenesis, with or without a functioning uterus. In the case of vaginal agenesis with a functional uterus, when menarche arrives, it will be marked by the occurrence of severe pain due to obstruction of menstrual blood flow out of the uterus in these women.

The following is a classification of female genital congenital anomalies which include congenital abnormalities in the uterus, uterine cervix and vagina (Figure 1 and 2) (Grimbizis *et.al*., 2013):



ESHRE/ESGE classification
Female genital tract anomalies

	Uterine anomaly		Cervical/vaginal anomaly
	Main class	***Sub-class***	***Co-existent class***
U0	Normal uterus		
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	
U2	Septate uterus	**a.** Partial **b.** Complete	
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate	
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity/no horn)	
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	
U6	Unclassified malformations		

C0	*Normal cervix*
C1	*Septate cervix*
C2	*Double 'normal' cervix*
C3	*Unilateral cervical aplasia*
C4	*Cervical aplasia*
V0	*Normal vagina*
V1	*Longitudinal non-obstructing vaginal septum*
V2	*Longitudinal obstructing vaginal septum*
V3	*Transverse vaginal septum and/or imperforate hymen*
V4	*Vaginal aplasia*

U	***C***	***V***

Associated anomalies of non-Müllerian origin:

Drawing of the anomaly

Figure 1 and 2. ESHRE/ESGE classification of uterine anomalies: schematic representation (Class U2: internal indentation >50% of the uterine wall thickness and external contour straight or with indentation <50%, Class U3: external indentation >50% of the uterine wall thickness, Class U3b: width of the fundal indentation at the midline >150% of the uterine wall thickness) (Grimbizis *et.al*., 2013).

VAGINOPLASTY PROCEDURE WITHOUT SURGERY

The management of Müllerian anomaly includes both non-surgical and surgical procedures. Success of the nonsurgical procedure is dependent on patient motivation and strict compliance. If dilatation is unsuccessful, operative vaginoplasty is indicated (Pangastuti *et.al.*, 2020; Pangastuti, *et al*., 2021a).

Frank procedure vaginoplasty

This procedure involves progressive invagination of the vaginal dimple and gradual dilatation. The success rate is quite good, reaching 85–90%. It may take months to produce a vagina of adequate depth and diameter. Appropriate counseling needs to be carried out considering that the dilatation procedure must be carried out in a disciplined and independent manner by the woman concerned (Breech, L.L. (2007).

Ingram procedure Vaginoplasty

This procedure is a modification of Frank's procedure. The dilator is specially designed in an integrated form as a bicycle seat, which must be used at least 2 hours daily at 15-30 minute intervals, to achieve desired vaginal depth and diameter. The size of the dilator can be increased every month, as needed (Breech, L.L. (2007).

VAGINOPLASTY SURGERY AS A TREATMENT OF MÜLLERIAN ANOMALIES

Vaginoplasty surgery is a reconstruction procedure that can be performed on women of all ages, from children, teenagers to adults. Vaginoplasty aims to form form the vaginal canal including the vulvar area, a 'new vagina' or neovagina that can function in penile penetration during sexual activity, as well as a way to drain menstrual blood in cases with a functional uterus (Pangastuti *et.al.*, 2020; Pangastuti, *et al*., 2021a).

There is no best procedure, but the first surgical procedure should be as good as possible to succeed, to prevent subsequent surgical procedures that usually become more difficult. Surgical procedur selection depending on the anatomical and psychological condition of the patient, family or partner support, surgeon's skill and experiance, tool support. For procedures that may require vaginal dilation (preoperatively and/or postoperative dilation), patients should be educated about the process of dilation and be mature enough and prepared to dilate postoperatively.

As one of the surgical procedures for the treatment of Mullerian anomaly, vaginoplasty has been performed since ancient times by many experts around the world. There are several types of vaginoplasty surgery, such as Abbe-McIndoe vaginoplasty, William vaginoplasty, Vechietti procedure, intestinal vaginoplasty, and others. These various procedures have their respective advantages and disadvantages. The choice of procedure is based on the condition of each case, in order to

obtain a satisfactory surgical result and can function throughout the woman's life.

From the data obtained in Yogyakarta Indonesia, there are 57 surgical procedures during the past 3 years. In addition to vaginoplasty using a sigmoid colon graft in 20 cases (36.36%), vaginoplasty was also performed using a pull-through method in 4 cases (7.02%). The surgery was performed using the abdominal laparotomy and vaginal routes (Pangastuti, *et al*., 2021a).

Abbe-McIndoe vaginoplasty

This procedure creates a channel in the connective tissue between the bladder and rectum, using a split-thickness skin graft (most commonly from the buttocks area) to cover the neovaginal canal that forms. During its development, several modifications were made, including using the human amnion, peritoneum (Davydov), or buccal mucosa (Ozgenel & Ozcan) (Breech, L.L. (2007).

The Counseller-Flor vaginoplasty

This is a modification of McIndoe technique. Using foam concrete formed for the vaginal cavity, then covered with a condom, then the skin graft is placed over the mold. This surgical procedure should be continued with dilation for the first 3 months after the procedure, and every night, unless regular intercourse occurs (Breech, L.L. (2007).

Vaginoplasty with amniotic membrane graft

Vaginoplasty procedure using amniotic graft is a technique that is relatively easy, inexpensive, and quite safe, does not require special materials or tools, so it is the right choice for cases of vaginoplasty surgery for vaginal agenesis in developing countries. The epithelialization process of the neovagina will be fully formed in 60-90 days after surgery, and the neovagina is ready to be used for sexual activity (Piazza, 2021).

The evaluation using vaginometry before and after surgery obtained good results. From the condition before surgery with vaginal length or depth from none to a maximum of 2-3 cm, after surgery the vaginal length became an average of 7-8 cm. The results of this surgery, after dilatation, as well as procedures to enlarge and deepen the neovagina, can provide satisfaction in sexual activity. Evaluation of the neovaginal epithelium reveals an epithelial shape that has characteristics similar to that of the vaginal epithelium (Piazza, 2021).

The McIndoe-Banister technique of vaginoplasty using an amnion graft allows the creation of a neovagina with a neoepithelial lining similar to that of a normal vagina. Amniotic graft serves to coat the surface of the neovagina, which in turn will shorten the healing period of the tissue. The amniotic membrane used to cover the neovagina undergoes a metaplastic process within 60-90 days after the surgical procedure (Piazza, 2021).

Williams vaginoplasty

This procedure uses skin and musculocutaneous flaps. A horseshoe-shaped incision is made at the vulva, extending across the perineum and up the medial side of the labia to the level of the external urethral meatus. Some of the advantages of this procedure are its simple technique, no serious local complications, faster recovery, easy postoperative care, and the possibility of eliminating the use of postoperative dilators.

Modified Creatsas Williams vaginoplasty

Modified Creatsas Williams vaginoplasty begins with the procedure of cutting the hymen with diathermy, then a U-shaped incision is made that extends across the perineum and upward to the external urethral opening, with a lateral dilation of about 4 cm. After the tissue has been mobilized, a first layer of interrupted suture is performed on the inner skin edge of the formed neovagina using absorbable sutures. Next, a second layer of suture with the same thread is performed to approximate the subcutaneous fat and perineal muscles. The outer skin is sutured with interrupted sutures also using absorbable sutures (Creatsas and Deligeoroglou, 2007).

Vecchietti laparoscopic vaginoplasty

The report of Wang, *et.al* conveyed from the Vecchietti laparoscopic vaginoplasty procedure that was carried out, it was found that this procedure was relatively safe and effective as a surgical method to

manage cases of congenital vaginal agenesis. This procedure can be an alternative variation of neovaginal surgery to obtain anatomical structure and function improvement according to the expected target, giving satisfaction to the patient's sexual function (Wang, *et.al*., 2021).

This surgical technique will form the neovagina in 7-9 days. Special equipment is required, namely a traction device that provides constant traction on the olive, a ligature carrier, and an olive-shaped vaginal dilator suture on the perineum (Breech, L.L. (2007).

The evaluation carried out on 79 cases after 30 months postoperatively obtained data for an average neovaginal length of 10.44 cm and an average neovaginal width of 1.30 cm. Functional efficacy reached 92.41%. There is no statistical difference in individual anatomical satisfaction or in measuring sexual function using the Female Sexual Function Index (FSFI). However, evaluation of the Female Genital Self-Image Scale showed significantly lower scores in these patients undergoing vaginoplasty (20.14 ± 3.05 vs. 22.95 ± 2.12; $p < .001$). There were no severe perioperative complications other than 1 case with mild bladder injury and 1 case with transient fever (Wang, *et al*., 2021).

Laparoscopic Davydov Vaginoplasty

The neovagina in this surgery was formed by pulling on the peritoneum, with good results. Peritoneal dissection was performed, clamped and pulled distally to be sutured to the introitus. Purse-string closure of the

peritoneal apex by laparoscopy. It is necessary to use a stent to prevent postoperative stenosis (Breech, L.L. (2007).

Wharton-Sheares-George vaginoplasty

George has modified the Sheares technique. The procedure is quite simple, does not require special surgical equipment, but is safe and effective. The results of surgery with this technique are very satisfactory both anatomically and functionally, in addition to a fast recovery process so that the hospital stay is shorter (Schätz, *et al*., 2005). One of the advantages of this procedure is the lower cost of treatment and surgery, thus reducing the burden on the hospital.

From the literature, it is stated that the average neovaginal length reaches 8.3 cm while its width is 3.3 cm. There were no complications during or after surgery. Similarly, no incidence of neovaginal prolapse was reported. Patients get satisfaction in general, both physically and psychologically, and especially in the achievement of sexual activity after this vaginoplasty surgery. As with other surgical outcomes of vaginoplasty, this method requires efforts to prevent neovaginal contractions. The epithelialization process can take up to several months to achieve complete healing, starting from the distal side of the neovagina until it reaches the apex. Neovaginal dilatation procedures that require adherence are sometimes necessary for the life of the patient (Kussel, *et al*., 2016).

The Wharton-Sheares-George vaginoplasty procedure provides a satisfactory alternative as a surgical procedure in cases of vaginal agenesis of MRKH syndrome (Schätz, *et.al*., 2005).

Intestinal Vaginoplasty

The grafts used are usually from the jejunum, ileum, cecum, or segment of the sigmoid colon. The most commonly performed intestinal vaginoplasty is using the sigmoid colon. This surgical procedure is quite complicated, requiring high operator skills. Surgery is expected to create a vagina that can form and function well for the rest of the patient's life. Surgery is performed using vaginal and abdominal access, with an aproscopic or laparotomy procedure (Breech, L.L. (2007).

Sigmoid colon vaginoplasty

There were a total of 26 cases of vaginal agenesis who underwent laparotomy sigmoid vaginoplasty surgery during 2010 to 2020 in Yogyakarta Indonesia. Twelve cases (46.15%) underwent surgery before 18 years of age. Five cases (19.23%) were of MRKH (Mayer-Rokitansky-Küster-Hauser) syndrome, a case (3.85%) with CAIS (Congenital Androgen Insensitivity Syndrome) while the other twenty cases (76.92%) had a uterus of various shapes. Ten cases (38.46%) had a normally shaped uterus, 9 cases (34.62%) did not have a normal uterine cervix, while one case (3.85%) had a didelphys uterus. Two cases (7.69%) that did not have a uterine cervix had only the left hemiuterine side. Sixteen cases (61.54%) had a history of previous

surgery, with the most previous vaginal procedures reaching 5 procedures (Pangastuti, *et al*., 2021b).

Eleven cases (42.31%) underwent isoperistaltic procedure, 14 cases (53.85%) underwent contraperistaltic, and 1 case underwent colon transposition procedure. Almost all cases used sigmoid colon as neovaginal graft, only 1 person used rectosigmoid graft. Complications during surgery were profuse bleeding and rectal injury in 2 cases (7.69%), and postoperative complications were wound dehiscence in the area of the laparotomy incision in 2 cases. All of these complications can be managed well.

Half of the twenty-four cases were married. Eight cases (33.33%) had the potential to become pregnant. The eleven cases (45.83%) that had sexual activity had good FSFI (Female Sexual Function Index) scores, meaning that there was no female sexual dysfunction. All cases with a functional uterus had normal menstrual cycles, no dysmenorrhea or obstruction of menstrual blood flow.

The sigmoid colon vaginoplasty procedure is the surgical technique of choice for vaginal agenesis cases, with or without a functional uterus. This procedure can be applied to all ages of women, has low surgical complications, with the postoperative result is a good neovaginal function in maintaining menstrual blood flow and penetration function in sexual activity (Pangastuti, *et al*., 2021b).

Postoperative Care

In cases where there is a high risk of neovaginal stenosis, including cases of pull-through vaginal formation, or following transverse vaginal septal resection, special treatment is sometimes required. These patients need to be treated with several days of bed rest for 3 to 7 days of stent use, depending on the surgical procedure performed. After the tissue has healed properly, then the use of vaginal dilators can be started with the aim of maintaining the expected neovaginal diameter.

Long-Term Follow-up

It should be noted the risk of endometriosis in patients with a history of obstruction or anomaly of the Müllerian duct. Because endometriosis is associated with infertility and uterine anomalies are associated with adverse obstetric outcomes, patients should receive long-term follow-up care to address any reproductive issues (ACOG, 2019).

CONCLUSION

Mullerian anomaly is a condition that requires special treatment. Vaginoplasty surgical procedure consists of several kinds of techniques. Each has advantages and disadvantages. Its application depends on the patient's condition, the availability of tools and materials, as well as the ability and experience of the operator.

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CHAPTER 10

GERIATRIC TRAUMA

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INTRODUCTION

Trauma is a major cause of mortality and decreased quality of life, accounting for nearly 10% of the global disease burden. Geriatric population is particularly more vulnerable to trauma due to decreased functionality of the body and gradually increasing dysfunction in major organ systems including cardiac, pulmonary, musculoskeletal and central nervous systems. The most common traumas experienced by geriatric patients include motor vehicle accidents, falls, pedestrian struck, and thermal injury. Elder abuse also is among the experienced elderly trauma. Severe traumas affect almost all major organ systems in elderly population, which is already at high risk of health related conditions due to the aging process. This chapter begins by addressing the epidemiology and pathophysiology of geriatric trauma. The most common causes of trauma are presented with a focus on falls that are the most frequent type of trauma in elderly people. The chapter continues with the general management of geriatric trauma cases prehospital and in the emergency department. High-risk injuries and special circumstances are given in detail and finally elder abuse/maltreatment is discussed.

1. EPIDEMIOLOGY

The elderly population is estimated to reach 83.7 million with a rate of 20.9% in the USA population (1). The European Union predicts an increase of individuals aged 65 years and above from 101 million in 2018 to 149 million by 2050 (2). This will bring a considerable increase in geriatric presentations to emergency services. In addition, the

increasing rate of this population is likely to have important effects on health of general population and health costs. Elderly patients are not damaged as much as young ones, although outcomes of these injuries may be more fatal. Age-related factors that contribute to these more fatal outcomes in geriatric patients include decreased physical reserves, preexisting comorbidities, underestimation of the injury severity and insufficiency in systemic compensation (3). In addition, elderly are at a higher risk of trauma due to their partly impaired motor and cognitive functions (4). Geriatric trauma patients are more likely to have poor prognosis baceuse of medication usage and complex comorbidities including obesity and OSA (5-8). Elderly people with obesity and OSAS, have a greater tendency to sleep deprivation in addition to other diseases (8).

According to a report published by the National Center for Health Statistics, traumas have become the seventh most common cause of mortality in older people (9). Most elderly patients with injuries get their traumas at home followed by streets and highways, workplaces and farms (10). Some authors have argued that specific geriatric trauma centers should be established (11). However, the incidence of geriatric traumas does not seem to increase.

2. PATHOPHYSIOLOGY

There are many anatomic and physiologic alterations associated with aging, which need to be better understood to diagnose and treat geriatric trauma patients effectively. Ageing process leads to significant changes in nutrition, muskuloskeletal, neurologic, cardiovascular, pulmonary,

gastrointestinal, genitourinary, hematologic, immune and endocrine systems (7, 12).

2.1. Ageing

Ageing is a process in which physiological integrity is lost progressively, causing dysfunction and increasing susceptibility to mortality (13). This complicated process leads to substantial anatomical and functioning alterations in almost all organ systems. The predominantly affected systems include respiratory system, circulatory system, musculoskeletal system, nutrition and metabolism and central nervous system (14).

2.2. Age-related Alterations

Aging process has a considerable impacgt on the physical functioninbh of the airways. Decays in teeth is frequent in elderly patients and poses a risk for dislodgement and then aspiration of a tooth during emergency procedures such as endotracheal intubation. Pharynx becomes more dry and fragile, requiring carefulness and attention while using laryngoscopy to avoid profuse bleeding. The risk of spinal cord injury increases in the case of cervical osteoarthritis. Excessive motion of the neck should be avoided for yis reason (15).

2.3. General Mechanisms of Geriatric Trauma

The most frequent causative factors of geriatric trauma events are shown in Figure 1.

Figure 1. The most common causes of geriatric trauma

Falls: Falls remain the most common geriatric trauma affecting approximately 30% of people ≥ 65 years old (16). Forty percent of traumatic injuries-related hospital admissions are due to falls (17). Falls are significantly more common among women than men (35.7 vs 24.6%) (18). Alterations in muscle strength, balance, gait, and vision loss related to aging are predisposing factors. Excessive alcohol consumption and drugs are also among predisposing factors for falls. Frequently used anticoagulants in geriatric patients cause lethal injuries even with minor traumas. Furthermore, falls of various types are the most freeqently encountered reason of brain injury in older people. Even minor falls may impair elderly's quality of life by causing anxiety due to fear of falling, which can lead to social withdrawal and depression. The most frequently encountered reasons for falls in elderly people are shown in Figure 2.

Figure 2. The most common causes of falls in elderly (19).

Motor Vehicle Accident: Traffic accidents involving elderly are increasing. Car accidents are among the main causes of trauma related death in elderly (20). Changes such as vision loss and impaired hearing and reduced vision at night due to aging, are the important factors contributing to the mechanism of injury and mortality from motor vehicle accidents. In addition, medical conditions and medications used may have negative effects on reaction time, attention and judgment.

Pedestrian Injuries: Older peoples' road-crossing behaviour indicates that they are trying to be more cautious. However, sometimes they appear to accept gaps that are not long enough to allow them to cross safely unless the approaching vehicle slows down. According to the 2015 data, in the USA 19% of all pedestrian deaths and 13% of injuries occurred in people aged 65 and older. In this age group, pedestrian strucks are among the most fatal mechanisms by 53% mortality rate (21).

Thermal Injuries: Mortality from burns is directly correlated with age. Elderly patients over 65 years old constitute between 13% and 20% of admissions to burn units, but this age group has the highest death rate among the overall burn population (22). Geriatric age group is disproportionately affected and advanced age is associated with poorer outcomes, partially because of thin skin and preexisting conditions. Severe burns can result in significant scarring and painful contractures, and victims of burns are at risk of developing depression and related psychiatric problems.

Elder Abuse: One of the most commonly encountered traumas in elderly people is abuse by younger ones. Elder abuse is under-reported with an increasing incidence. It can present in many ways, such as physical, financial, emotional, sexual, and neglect. In many situations the abuser can be their very close family member as well as a foreigner for intentional purpose to give harm to these people. Elder abuse is an issue that should be addressed in more details and is discussed under a separate title below.

3. CLINICAL FEATURES AND APPROACH TO GERUATRIC TRAUMA PATIENTS

A rapid assessment and appropriate intervention to life-threatening conditions in elderly trauma patients should be performed promptly. The evaluation should be the same as the other age groups and include prehospital management, triaj, and management of elderly in the emergency department. Undertriage of gertiatric patients with trauma is an important problem that frequently begins during the prehospital

evaluation. Studies have shown that patients treated in a trauma center have improved outcomes. The triage criteria by the American College of Surgeons recommend to care for patients aged 55 years and over in a trauma center (7). Prehospital care providers must maintain a high clinical suspicion in terms of serious injury regardless of the underlying mechanism. General management of the geriatric trauma patients must be performed considering their unique physical condition and associated comorbidities. A multidisciplinary approach is essential as geriatric patients may have a wide spectrum of manifestations. The majority of elderly patients with trauma can heal, but the healing period will last longer than young ones. Many geriatric trauma patients remain in hospital for prolonged periods and even when discharged, tend to have a residual dysfunction (23, 24).

3.1. Triage and Prehospital Management

Triage of elderly trauma patienst can be made according to the "triage decision scheme at field", which a publication of the American College of Surgeons Committee on Trauma as a guidance for prehospital triaging (Figure 3). A lower-level triage than required is more common in geriatric patients (3). In 2011 updated version, two important items were added to the scheme to avoid under-triage:

- SBP < 110 may indicate shock after 65 years old.
- Some low-effect mechanisms such as falls at ground level may cause severe injury.

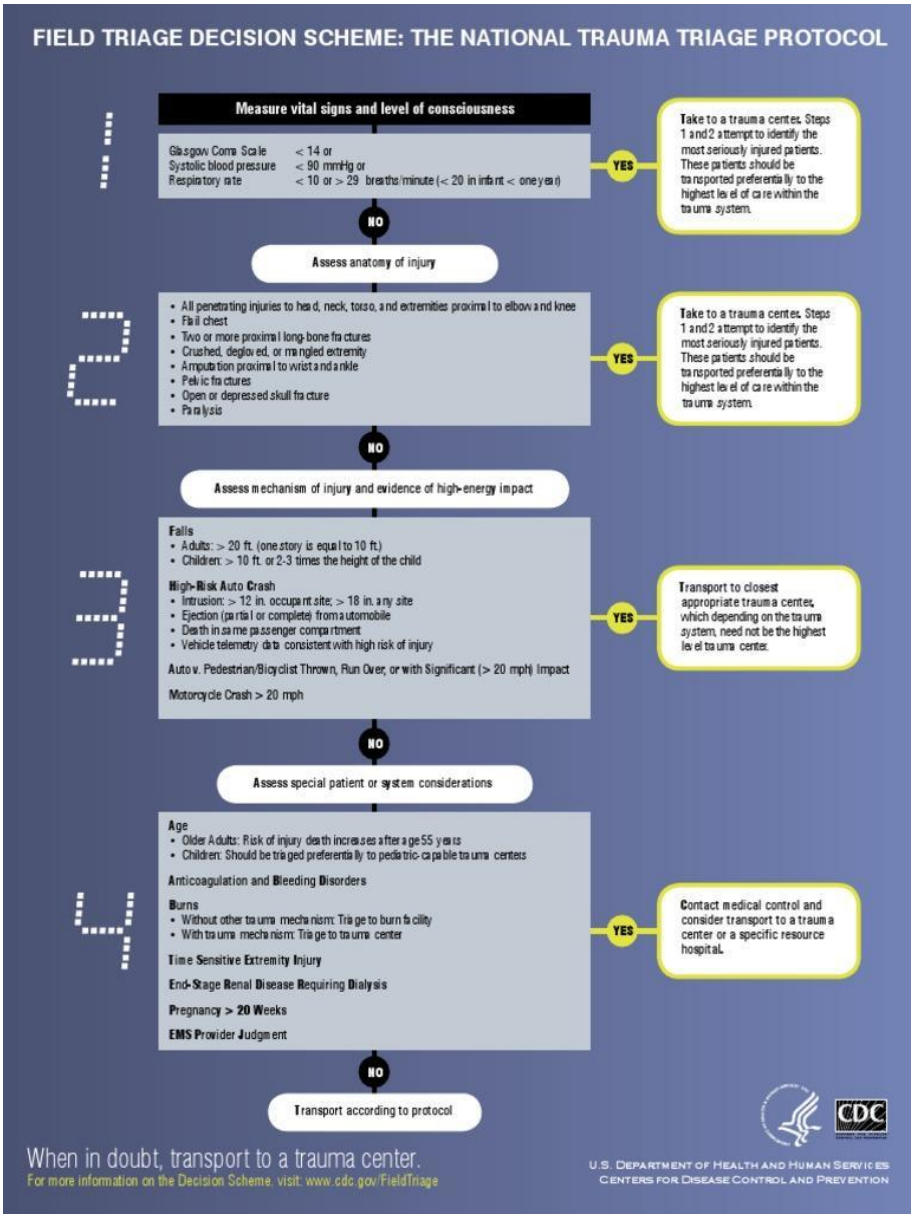

Figure 3. Pre-hospital triage of injured patients-American College of Surgeons Committee on Trauma (ACS-COT), United States, 2011 (25).

Some authors argued that geriatric patients who met these criteria should be directed to the trauma center (26). It seems that elderly patients benefit more from triage centers with considerably improved results (27). However, unfortunately only a few elderly patients with trauma are directly triaged to major trauma centers and these patients are more likely to be initially seen by junior physicians (28).

3.2. Management of Elderly Patients in Emergency Room

Management of injured geriatric patients in the emergency department is challenging. According to the National Vital Statistics report from the USA, among geriatric trauma victims, those aged 75-85 years have the highest death rates with 86.1-296.6 deaths per 100,000 (29). On the other hand, older trauma victims have higher rates of morbidity and mortality as well as longer hospitalization and higher resources consumption compared to younger trauma victims (30).

In the primary assessment of elferly patients in emergency room vital functions, ABCDs are evaluated rapidly, life threatening conditions are identified and the necessary interventions are made. The first goal is to establish and maintain a patent airway to provide adequate oxygenation. In order to prevent damage to the spinal cord, the neck should not ber moved excessively. Early administration of oxygen supplement is crucial (15). Head-to-toe assessment is then performed with diagnostic investigations. At this stage, physicians should concentrate on determination and treatment of injuries that were not recognized during the first assessment.

4. HIGH-RISK INJURIES

Serious complications following a trauma are likely to develop depending on the severity of the injury, although even falls at ground-level falls can lead to severe injury and mortality in these patients (31). The most common high-risk injuries in geriatric trauma victims are as follows:

4.1. Head Injury

A number of physiological changes occur with ageing that predispose elderly patients to hemorrhagic complications following head injury. These changes include cerebral atrophy, hypertension, reduced cerebral auto-regulation, cerebrovascular atherosclerosis, increased monoamine oxidase B concentration, ageing mitochondria, reduced superoxide dismutase concentrations and increased superoxide production (32). These age-related structural alterations put geriatric patients at a higher risk for developing traumatic brain injury with falls being the primary mechanism of head injury by 81.8% and cause of mortality by 54.4% (25).

Evidence suggests that approximately 30% of intracranial injuries do not present with reliable clinical findings (33). Some older patients better tolerate intracranial hemorrhage than young patients, leading to underestimation of the severity or extent of head injury. If imaging outcome will affect the medical decision, non-contrast enhanced CT should be performed in all geriatric patients presenting with head injury (28). Rapid neurological decline should be taken into account in

geriatric trauma patients. On the other hand, antiplatelet and anticoagulant medications in elderly may have negative consequences. Anticoagulants received during head injury event increases the chance for developing intracranial bleeding (34). In a study, it was found that warfaring therapy received during head injury significantly raises the rate of mortality, especially after 70 years of age (35).

4.2. Spine Injury

Two most frequently encountered spinal injuries during a trauma are cervical spine injury and thoracolumbar spine fractures.

Cervical spine injuries: These injuries are more frequently seen in older ages with an increasing incidence (36). Most geriatric cervical spine injuries are secondary to falls (>60%). C-spine fracture is more common in elderly patients after ground-level falls. However, they can also occur due to any traumatic mechanism such as motor vehicle accidents and assault (37). The best diagnostic test to assess for cervical spine injury is CT in the emergency setting. Management of cervical spine injury in geriatric patients is controversial and halo cast immobilization with reduction, includes rigid collar immobilization without reduction, and surgical management (38).

Thoracolumbar spine fractures: These fractures are generally related to osteoporosis in elderly. Approximately 50% of patients with thoracolumbar spine fracture are affected by osteoporosis, which promotes the development of spontaneous fractures due to vertebral compression. These fractures are mostly located in the thoracolumbar

spine. Among these, fractures due to anterior wedge compression are the most common type from the 10th thoracic vertebra to the 4th lumbar vertebra (T10 – L4) (39). Again, falls are the main mechanism ıf such injury in elderly patients.

For today there are two main treatment approaches for these fractures including conservative and surgical options. Surgical intervention indicated in severe burst fractures and unstable flexion distraction fractures. Whereas, conservative therapy including bed rest and bracing seems to be a more reasonable option in patients with intact neurologic status (3). Cervical spine in geriatric patients is best evaluated by CT scans.

4.3. Chest Traumas

These traumas lead to about 796,000 presentations to emergency departments in the USA alone each year (40). The most commonly encountered blunt chest traumas are falls and motor vehicle collisions. Blunt chest trauma accounts for 25% of traumatic deaths that contribute up to 50% of global mortality. These traumas are commonly associated with multiple organ damage that leads to catastrophic patient outcomes. The elderly people are more prone to chest trauma, which is associated with high morbidity and mortality. The mortality and risk of developing pneumonia significantly increase after 65 years of age. Comorbidities, osteoporosis and loss of muscle mass prompt the development of rib fractures and pulmonary contusions in geriatric population. Traumatic chest injuries are divided into four types:

1. Thoracic wall,
2. Lung,
3. Mediastinum, and
4. Diaphragmatic wounds.

However, due to the limited place these chest trauma types can not be presented in detail here. Clinicians should consider early ventilatory support in cases of pulmonary contusion as these patients are vulnerable to respiratory compromise. Considering the above mentioned risks, a detailed physical exam, supervision and early administration of oxygen and appropriate analgesics are highly recommended and can be life saving in these patients. In the image studies, plain X-rays may not reveal extent of the injury, requiring progression with CT scans. Life threatening chest trauma in older people should prompt admission in the ICU for close supervision.

4.4. Abdominal Trauma

Abdominal examination is often less reliable and more challenging in geriatric trauma patients, because pain sensation is decreased and laxity of abdominal wall musculature is increased in geriatric patients. Tachycardia response against hemorrhagic shock may be overlooked (15).

Although abdominal injury has the same characteristics to young patients, its management is controversial. Close observation and high index of suspicion must be maintained in order to avoid under diagnosis. Patients who sustain blunt abdominal trauma can be assessed

through the Extended Focused Assessment with Sonography for Trauma (eFAST) algorithm in order to determine the presence of intra-abdominal fluid (41). CT is the gold standard diagnostic tool. The risk of retroperitoneal hemorrhage is high in case of chronic anticoagulant usage. Particularly elderly patients with pelvis or hip fracture should be evaluated for hemorrhage with contrast enhanced CT scans. Although abdominal traumas usually requires conservative approaches, operative approach seems to be more commonly applied in elderly patients compared to young ones. However, the balance between risk and benefit must be assessed well, because mortality following laparotomy increases with age (42). An emergency surgery score has been recently developed for this purpose. The scale consists of 5 clinical variables and can help prediction of 1-year mortality, facilitating preoperative evaluation. However, it has still not been validated in geriatric patients who underwent trauma (43).

4.5. Musculoskeletal Injury (2820)

Elderly people often experience fractures that can cause severe pain, disability, loss of independence and worsened quality of life. The increased risk of fractures in elderly may be caused by osteoporosis, sarcopenia, and more commonly frailty with ageing.

Pelvic fractures: Ground-level falls with low-energy may lead to fractures in geriatric patients (44). In general, no complications ccur due to trauma in patients with pelvis fractures because of minor trauma,

although there is an increase in morbidity and mortality in these fractures resulting from accompanied bleeding and other damages.

AP pelvic chest radiograph should be ordered during the initial assessment. On the physical exam, tenderness following pelvic trauma suggests a possible pelvic fracture. In stable patients, CT scan may be obtained. Arteriography and embolization can be carried out in the case of an active bleeding detected. In the management of pelvic fractures in elderly, resuscitation, skeletal stabilization and hemorrhage control are critical steps to manage these patients in emergency service.

Proximal femur fractures: these fractures in elderly usually result from a fall, low-energy pattern or injury. Proximal femur fractures in geriatric patients may lead to immobility, permanent dependence and mortality. The likelihood of proximal femur fractures increases in patients aged over 80 years and nearly 80% of these patients are women (45). The risk of experiencing fractures in this population depends on the number of falls and bone mineral density (BMD). Medical history and clinical presentation are usually sufficient to make the diagnosis of most hip fractures. However, in patients with a nondisplaced or incomplete femoral fracture, clinical signs and symptoms may be minor on presentation to the emergency department, while in displaced fractures of the femur neck, the limb underwent shortening and external rotation, causing severe pain with attempts to move the hip result in increasing pain.

The initial assessment of an elderly patient with a proximal femur fracture includes standard AP and lateral X-rays of the hip. However, nondisplaced or incomplete fractures may not be noticed on plain X-rays and will be apparent on CT.

5. ELDER MALTREATMENT AND ABUSE

Elder abuse and maltreatement is a crucial human right and public health issue associated with morbimortality all over the world. It has been reported that approximately 10% of elderly people experience various forms of elder abuse in the USA (46). The most common forms of elder abuse are presented in Figure 4.

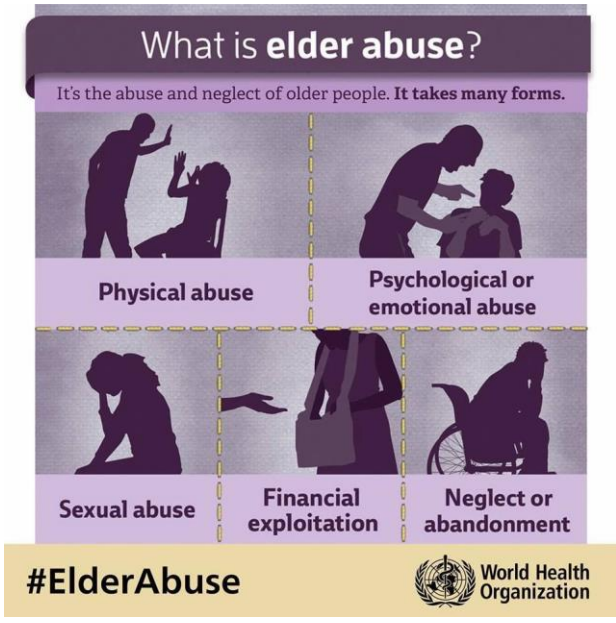

Figure 4. Various forms of elder abuse (47).

Elder abuse is often not recognized and these statistics represent underestimation of the extent of these events. Elder abuse is one of the

most serious geriatric trauma events with both physiological and psychological consequences. The risk factors of elder abuse include female gender, relationship with the abuser, being socially isolated and the victim's personality (48).

Screening for elder abuse should be performed in geriatric trauma patients, especially in those who do not want to report abuse because of fear or elderly patients with cognitive impairment.

CONCLUSION

The number of elderly trauma patients presenting to emergency departments steadily increase and will continue to indicate the need for better triage and care of this group of patients. Furthermore, prevention programs addressing risk for falls and other injuries need to be better included into the care of elderly patients admitted to emergency departments. Although there are numerous studies in the literature investigating geriatric trauma utilizing trauma registry data of emergency departments, it seems difficult to draw firm conclusions from these observational studies. There is an urgent need for further studies in the areas of specific perspectives of trauma prevention, care, prehospital triage, and urgent intervention to traumatic patients to improve both short and long-term outcomes.

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CHAPTER 11

OVERVIEW OF ARTERIOVENOUS FISTULA COMPLICATIONS

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INTRODUCTION

Kidney failure is a public health problem that most deeply affects the daily lives of patients who create very serious social problems all over the world. The number of patients with end-stage renal disease (ESRD) who need renal replacement therapy, especially hemodialysis, is increasing day by day. It has been reported that there are 2.5 million patients worldwide, according to the figures from the countries registered in the 2015 data (1). Among the renal replacement therapies, the most effective is hemodialysis. The first option for hemodialysis vascular access is the creation of an autogenous arteriovenous fistula (AVF). In line with the principle of venous system protection, the most distal vein should be used. The second option is arteriovenous graft created with synthetic graft. The third option is a tunneled subcutaneous central venous dialysis catheter (2,3,4). Arteriovenous fistula is the first choice because it has a lower incidence of complications compared to other methods. The risk of infection increases with the long use of catheters and grafts. Also, the need for repetitive intervention is higher. This results in long hospital stays and high costs (5). Basically, it is reported that avf provides high survival (6,7,8). Although there are different rates in different centers depending on the surgical technique, the training of the surgeon, and the facilities of the center, the rate of use of AVF varies between 40% and 80% (9). Needle entry technique may affect the occurrence of complications and long-term use of the fistula. Trained personnel should be used for this (3,10). By standardizing the AVF in the most effective way, we should create a

future-oriented perspective that provides low complications and long-term patency.

AVF COMPLICATIONS

AVF complications can be classified as early and late events.

Primary patency; AVF is the best clinical outcome in which adequate flow is achieved without the need for any additional surgical intervention (11,12).

Assisted primary patency;The time that patency is achieved with the intervention after the first occlusion of the venous access

Secondary patency; It is the time elapsed, including all interventions, until the venous access ceases to form.

İmmediate failure; It is the insufficiency of flow velocity due to surgical errors, insufficient vessel diameters and vessel stenosis.

Primary failure; Permanent insufficiency of the AVF before it is suitable for dialysis. Inappropriate remodeling in the first 3 months can also be called.

Secondary failure; Failure of AVF after reaching dialysis eligibility criteria (13,14).

Early dysfunction of the AVF is caused by both pre- and acquired anatomical anomalies and hemodynamic dysfunctions.

İnflow defects are related to arterial wall quality, such as thinness, age-related atherosclerosis, diabetes(15,16). Outflow defects are associated with venous anomalies such as sclerotic vessels or thromboses (17,18,19,20,21).

Endothelial dysfunction seen with neointimal hyperplasia can cause stenosis or aneurysm together with vascular remodeling. The wall shear stress (WSS) formed by the blood flow in the vascular wall is one of the major factors in the pathophysiology of atherosclerosis (22,23,24).

The placement of an artificial arteriovenous anastomosis creates an abrupt flow from the high-pressure vascular bed to the low-pressure capacitance system. Oxidative stress, activation of peroxynitrite, release of matrix metallopretinases and inflammatory cytokines play a role in neointimal hyperplasia developing in the vein (25,26).

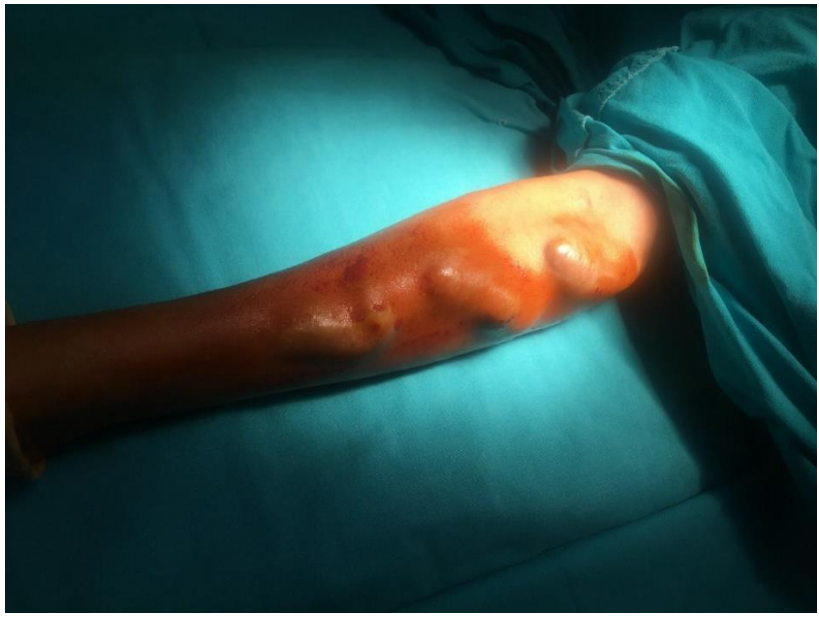
Stenoz

Vascular lumen narrowing occurs due to atherosclerotic plaque, neintimal hyperplasia, and obstructive thrombus. There are 3 types of venous stenosis.

1. Juxta anastomotic stenosis: It affects the first 2 cm of the anastomosis and accounts for 80% of all venous stenoses. Stenosis due to reactive

neointimal hyperplasia causes early fistula loss. In this variant, the contraction is stubborn.

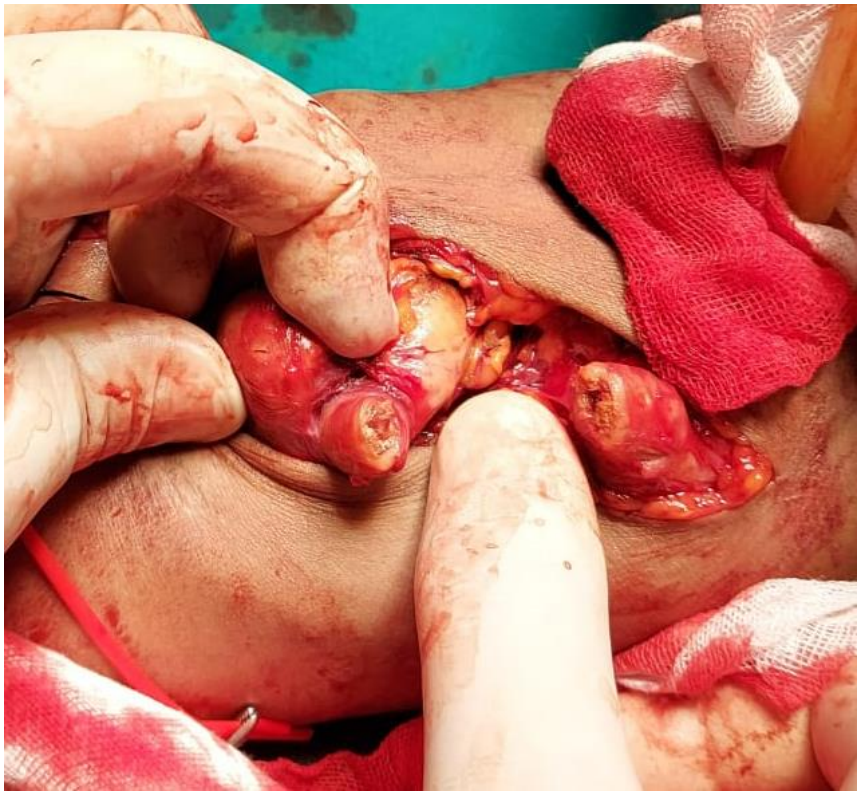
2. The long-term results of percutan transluminal angioplasty are not promising. Even drug-eluting balloon angioplasty continues to require surgical repair again.
3. Anastomotic strictures: It occurs as a result of reactive hyperplasia or surgical errors. It is the most common cause of maturation defect and premature AVF loss (16,27).



Picture 1. Stenosis and Aneurysm(44)

4. Stenosis of the venipuncture segment is a typical complication of a mature fistula. The length of the stenosis can be short or long. Short strictures are a late complication and are localized between the two entrances. Conversely, multiple or enlarged areas of stenosis are the fibrotic response to repetitive vein access. Angioplasty is the first

choice treatment option in such strictures. However, surgical correction with bypass or patch may also be required (28).



Picture 2. Surgical view of intravascular stenotic segment(44)

Stenosis develops in 30% of prosthetic grafts. This complication is frequently seen on the venous side. Anastomotic stenosis consists of reactive neointimal hyperplasia seen due to surgery, endothelial damage, incompatibility between prosthesis and native vessel, and WSS variations. Tributary artery stenosis is rare. As a result of atherosclerotic degeneration of the vessel wall in elderly patients, non-critical stenosis can become critical with dilatation and remodeling of the arterial lümen. (16,29,28)

Many factors can affect the severity of mature AVF and graft stenosis. The length of the stenosis is important. Because, according to Poisieulle's law, the length of the vessel is inversely proportional to the flow. In addition, hemodynamic factors such as the diameter of the stenosis, vein elasticity, cardiac output, blood pressure, aneurysm, and geometric anomalies may affect the long-term function of the AVF. (29)

If the lumen narrowing is more than 50% compared to adjacent vessels on angiography, it is considered critical. (16)

Maturation Defect and Early Failure

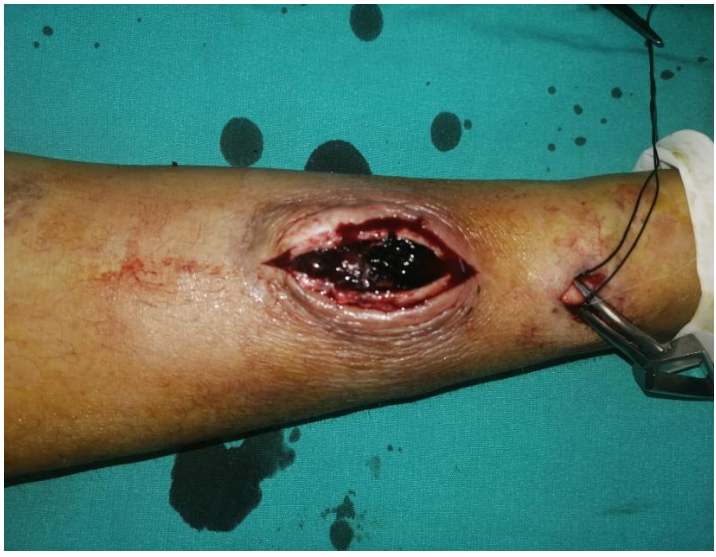
The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K_DOQI) guidelines determine dialysis eligibility criteria. These pass as 6 rules. Vein diamater ⩾ 6mm, blood flow rate ⩾ 600mL/min, vessel depth<0.6 cm, and venopuncture segment length > 6cm. (30,31) According to the Fistula First Breakthrough Initiative (FFBI) rule, the flow rate varying between 300-800 mL/min is accepted as a normal vascular tract (32). The hemodialysis fistula maturation study group considers that the minimum vessel diameter of ⩾ 4 mm and/or flow rate ⩾ 500 mL/min are appropriate measures for hemodialysis. In cases where both of these criteria are met, the probability of fistula compliance is considered to be >95%. If none of these criteria are met, the dialysis compliance rate is only 33%. (32)

With the decrease in pressure, the blood flow rate increases in the maturation period of the distal radial avf. Stress tests (reactive hyperemia, Allen's test) should be performed to accurately determine the flow rates of the radial artery before creating the AVF.

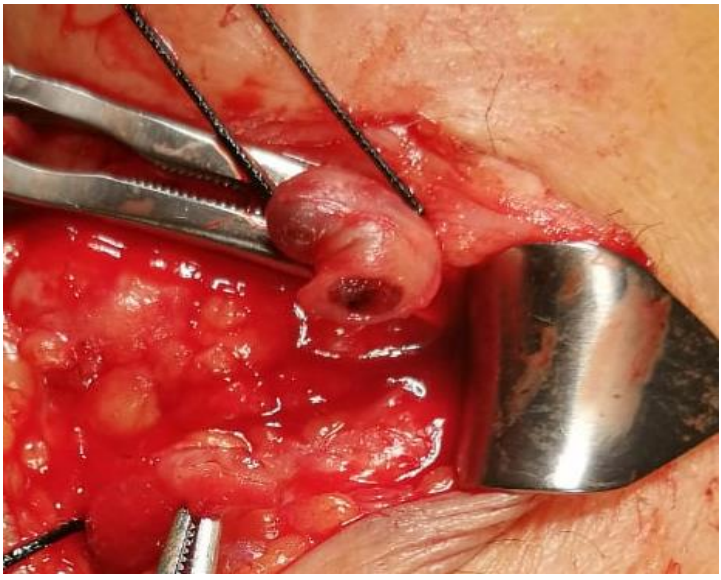
If the brachial artery flow rate does not increase during the maturation process, it causes an explosive acceleration (PSV>2.5-3.5m/s) in the peri-anastomotic segment. At this stage, collateral vein development and insufficient vein dilatation occur. Late failure occurs some time after the first cannulation, but is usually caused by non-critical stenosis. The current decreases progressively.

Early and Late Thrombosis

It can be seen immediately after surgery or in the following years. Thrombosis may be caused by rotation of the vessel or poor anastomosis. Solving technical problems, thrombectomy and medical treatment should be applied. Intima ischemia may develop in delayed thrombosis. With early thrombectomy, the anastomosis is opened, the artery and vein are cleaned with 3F fogarty, then irrigation is performed with heparinized saline and the anastomosis is closed again. If the trill is not felt after anastomosis, a new fistula should be created more proximal. Delayed thrombosis results from stenosis of the anastomosis due to intimal hyperplasia. Or it is the scarring caused by repeated insertions. Low blood pressure, loss of fluid, tendency to clot, pressure on the vein increase the risk of thrombosis. After the fistula is opened, stenosis may develop in the vein part just distal to the anastomosis in the late period. This short segment can be enlarged with patch angioplasty.

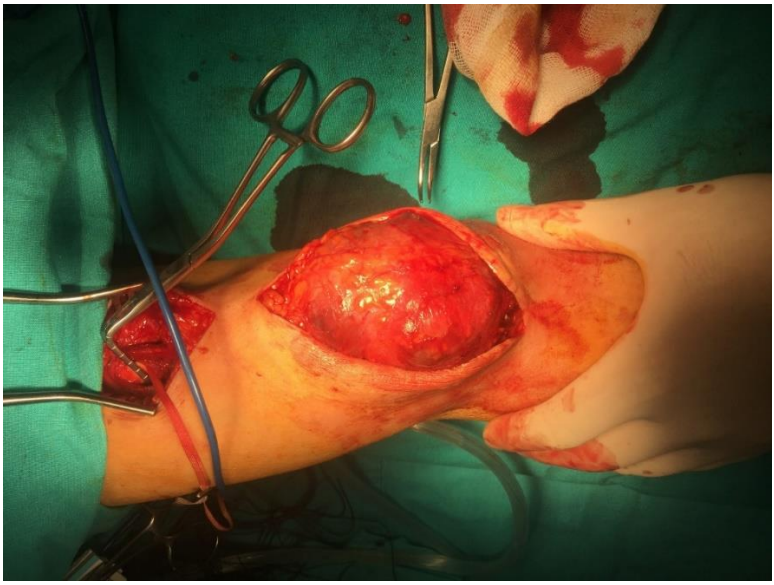


Picture 3. Surgical view of ıntravascular acute thrombuosis



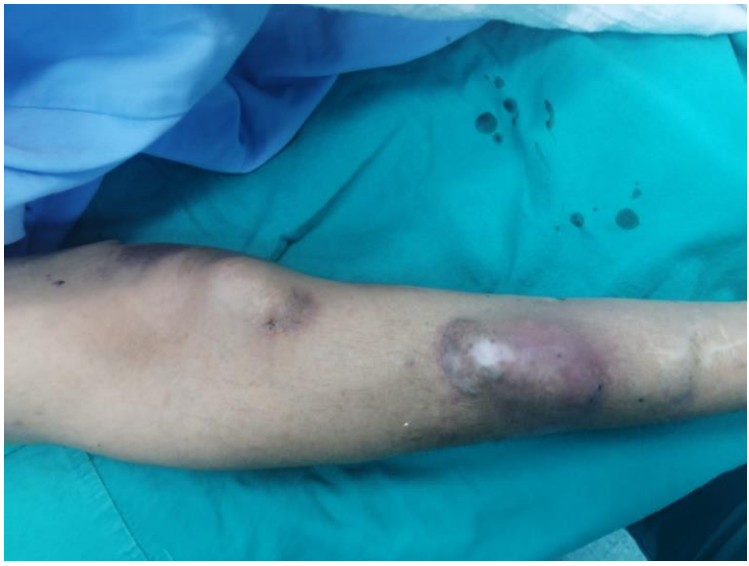
Picture 4. Surgical view of intravascular chronic thrombosis (44)

Aneurysm Hematoma Pseudoaneurysm Seroma



Picture 5. Surgical view of aneurysm (44)

Damages such as aneurysm, hematoma and pseudoaneurysm may occur on the wall of the outgoing vessel due to repeated interventions. The aneurysm may be in the form of fusiform or saccular dilatation. Hematoma and pseudoaneurysm occur in posttraumatic conditions. The hematoma lies outside the vessel and is not continuous with the lumen. A pseudoaneurysm is a perivascular collection. Unlike hematoma, it is continuous with the vessel lumen. Unlike an aneurysm, it does not have its own wall. It is limited by reactive fibrous tissue covered with endothelium. (33)



Picture 7. Pseudoaneurysm (44)

Seroma is an uncommon complication of prosthetic AVF grafting. A sterile and clear transudate serum accumulates in the connective tissue surrounding the graft within approximately 1 month after the graft is placed. Seroma is typically localized close to the arterial anastomosis. (34) Aneurysm and pseudoaneurysm appear pulsatile on physical examination, while hematoma and seroma are non-pulsatile. If the mass grows progressively and diagnosis is delayed, the overlying skin may appear thin and translucent, reddened, and ulcerated. If the mass grows progressively and diagnosis is delayed, the overlying skin may appear thin and translucent, reddened, and ulcerated. More often, the risk of rupture according to Laplace's law, such as aneurysm, irritates the artery and median nerve or causes venous thrombosis. (34)

For treatment, sequential aspirations are helpful. However, this may cause skin necrosis, graft thrombosis, and loss of vascular access.

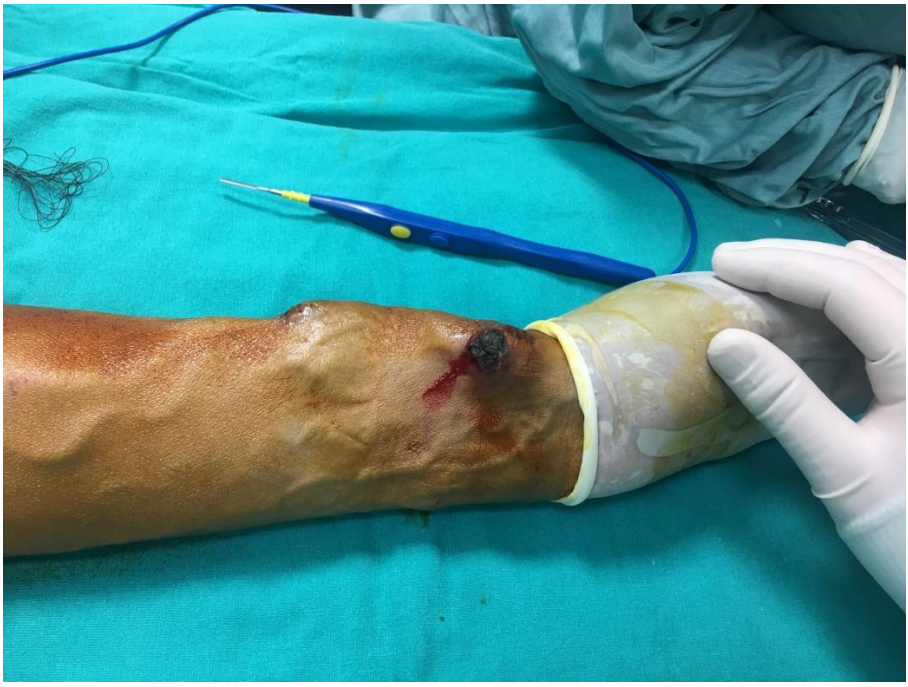
Surgical unloading and wrapping of the graft using microfibrillar collagen is rarely necessary.(33) Generally, pseudoaneurysm appears as saccular dilatation near the drainage vein wall, whereas true aneurysm appears as fusiform or saccular dilatation.

Aneurysm and pseudoaneurysm treatment depends on its location, size and which vessel it is in. In particular, small vein pseudoaneurysms may not need to be treated. If its growth is stable, it can be followed by clinical observation. Conversely, new, small pseudoaneurysms can be treated with 35-40 minutes of ultrasound probe compression. Percutaneous injection of bovine thrombin may be useful for rapid thrombosis and closure of the pseudoaneurysmatic cavity. (35) Major vessel thrombosis and allergic reactions are possible complications of this procedure. Arterial pseudoaneurysms, regardless of volume, will constantly increase due to high pressure and should always be treated surgically. Growth rate, infections and skin lesions increase the risk of rupture. Vascular surgery is an effective treatment approach for pseudoaneurysms and aneurysms of the arm arteries, prosthetic grafts or anastomoses, especially if there are skin complications. (35) Temporary stent graft placement should only be considered in the presence of ongoing bleeding or high-risk rupture awaiting surgical correction.

Infection

It is frequently seen at the dialysis port. They can cause thrombophlebitis, thrombosis, bleeding or false aneurysm. Strict aseptic rules should be applied in dialysis units for infection control. Infection

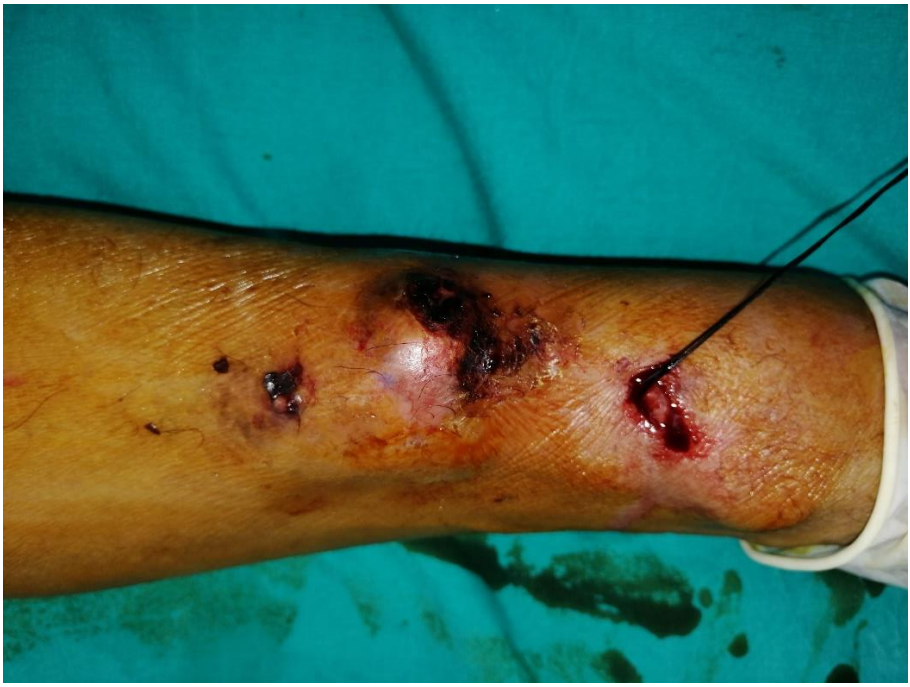
appears in the form of redness and swelling within 48 hours. Antibiotherapy is recommended. Other entries should be made away from the infected area. If no improvement is observed and if it becomes complicated, the infected segment is removed and bypass is performed with a vein graft. (36)



Picture 8. Infection (44)

Bleeding

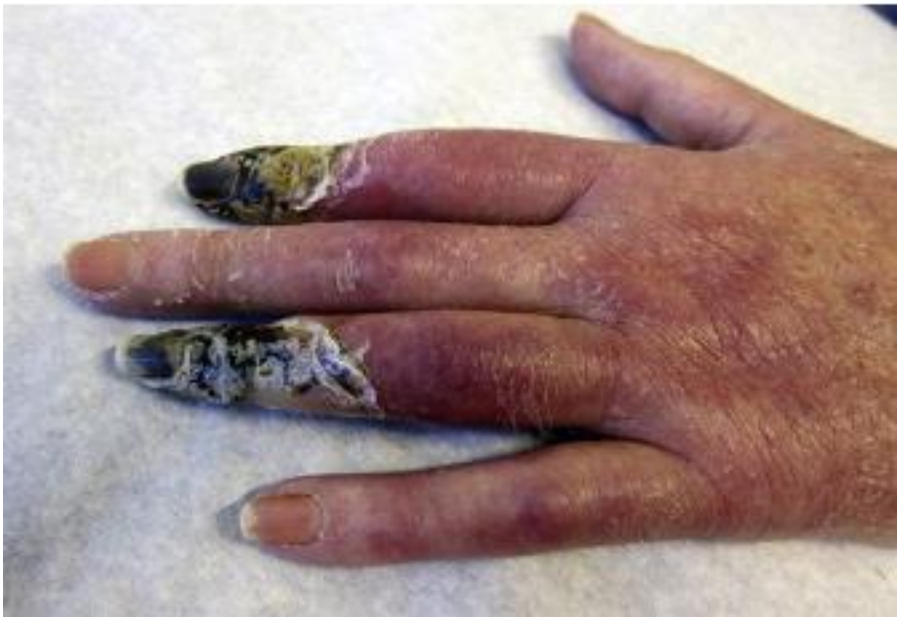
It is seen in two forms as primary bleeding or secondary bleeding. Primary bleeding occurs due to technical problems or bleeding disorder in the early postoperative period. Bleeding seen in late-stage infections is called secondary bleeding.



Picture 9. Bleeding (44)

Arterial Steal Syndrome

In the Steal syndrome, the blood that should feed the tissues distal to the artery passes to the vein to a large extent, causing the distal nutrition to be impaired. It is usually seen in more proximal fistulas. Symptoms such as coldness, pallor, pain, numbness are seen in the extremities. It is usually seen with excessive blood withdrawal during dialysis. Its treatment is based on narrowing the fistula or the vein after anastomosis.

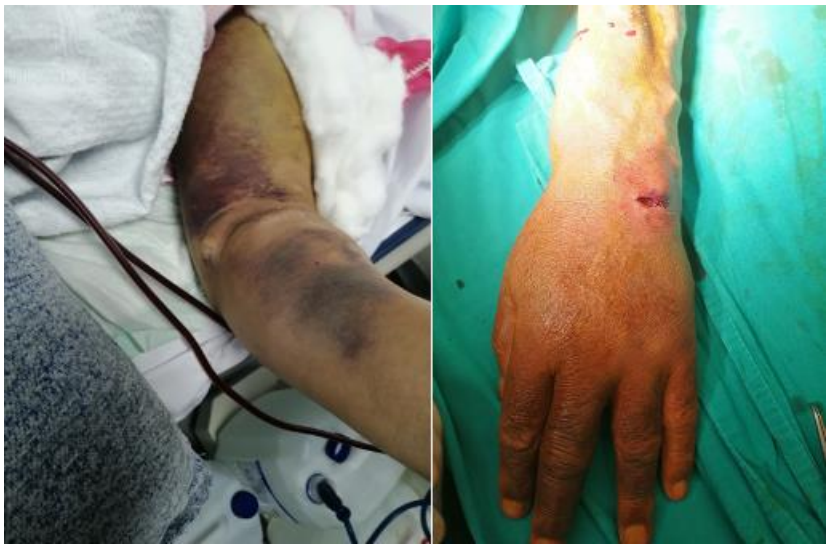


Picture 10. Steal sendrom(37)

Heart Failure

Optimal blood flow in the fistula is expected to be 350-500 ml/min. Peripheral A-V fistula opened in patients with normal cardiovascular system can be tolerated. However, in patients with heart disease, the hemodynamic load added by A-V fistula may not be tolerated. In this case, heart failure may develop. The risk of heart failure increases with the fistula flow rate above 500 ml/min. However, in patients with heart failure, fistula-related failure should be considered after checking whether conditions such as anemia, high blood pressure, and fluid balance are optimal. Cardiac index should be measured with the fistula open and closed. When heart failure due to fistula is considered, the flow should be reduced by revision.

Venous Hypertension



Picture 11. Venous Hypertension(44)

Venous hypertension presents with only venous dilatation, edema only, severe painful edema, and skin discoloration. Venous hypertension may occur in the index finger and thumb after radiocephalic arteriovenous fistula. Obstruction in the proximal vein may cause hypertension in the distal venous network. In case of ulceration and exacerbating pain, the distal vein portion can be ligated. Venous hypertension develops in the entire arm when fistula is formed in the arm with unrecognized subclavian vein stenosis. In its treatment, the fistula should be closed.

Conclusion

Hemodialysis in patients with chronic renal failure providing a comfortable and safe vascular access for AV fistula was first described in 1966 by James Cimino and Brescia. (38) AVFs are an easily accessible, low-cost vascular access route with few late complications.

They are formed as a result of subcutaneous anastomosis of the artery and vein in the forearm or upper arm, and after a few months, they allow hemodialysis with the enlargement of the vein and thickening of its wall.(39) Complications such as thrombosis, extremity edema, extremity ischemia, aneurysm, graft infections, heart failure or pseudoaneurysms can be seen in the late period due to errors in anastomosis technique, continuous repetitive injections, trauma and infection at the entrance site after arteriovenous fistula surgeries.(38) Aneurysmatic dilatations are the most common late complication in patients with arteriovenous fistula. Untreated AV fistula aneurysms often enlarge and produce distal ischemia as a result of venous hypertension or the steal phenomenon. Excessive dilatation and mobilization of the vein causes vessel wall damage and aneurysm formation. Errors in anastomosis technique, repetitive cannulation from the same area, infection, trauma are the factors that cause venous aneurysm development. Pseudoaneurysm usually develops at the site of repeated venous puncture, while true aneurysm occurs more often at the site of anastomosis. Eventually, it can cause skin necrosis and unstoppable bleeding. If the diagnosis is definite as a result of physical examination or CDUS scan, there is no need for angiography in the preoperative period. Angiography is useful when distal perfusion is impaired.(40) In the presence of ulceration, ischemia or skin infection, treatment indication occurs in patients.(41) Among the treatment methods, manual compression with CDUS, endovascular graft

implantation, thrombin injection and surgical repair or surgical closure of the fistula can be counted.(42,43)

As a result, complications may develop due to the opening or use of AV fistulas. Opening the AV fistula by using the anatomical segments carefully and then paying attention to the use of AV fistula while undergoing hemodialysis will be beneficial for the preservation of the patient's fistula. It is important to train the dialysis team on fistula use and follow-up for the protection of AV fistula in patients undergoing hemodialysis. In this way, early recognition of complications that may develop in patients and surgical intervention before infection or ulceration occur will be possible. Thus, the continuity of hemodialysis of the patient can be ensured from the same fistula with fistula sparing surgery after early diagnosis.

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44. Erciyes university operating room our own patient images

CHAPTER 12

CARDIOVASCULAR ASSESSMENT ON SURGERY

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INTRODUCTION

Perioperative assessment varies from the patient's disease and functional capacity to the type and duration of surgery and even the method of administration of the anesthetic agent. In general, the main mechanism is that the myocardial need is not met with the blood presented in the myocardium and that stress together with inflammation causes plaque rupture. Complications are more serious in patients with valvular regurgitation, heart failure, and coronary ischemia. My aim in this chapter is to prevent possible cardiac complications.

1. PRE-OPERATIVE EVALUATION

1.1. Surgical Risk for Cardiac Events

The type of surgery is also important along with the risk factors of the patient (Wirthlin, D. J. 1998). The surgical approach, which requires less invasive procedures, reduces mortality. This is because there is less body fluid shifts and electrolyte changes and less blood loss. Thus, less stress response occurs. According to the mortality rate in the first month after surgery, surgical interventions have been classified as low risk, intermediate risk and high risk (table 1).

Table 1. Surgical risk estimate according to type of surgery[1]

Low-risk: <1%	İntermediate-risk: 1-5%	High-risk: > 5%
Superficial surgery Breast Dental Endocrine: thyroid Eye Reconstructive Carotid asymptomatic (CEA	İntraperitoneal: splenectomy, hiatal hernia repair cholecystectomy Caroid symptomatic (CEA or CAS) Peripheral arterial angioplasty Endovascular aneurysm repair Head and neck surgery	Pneumonectomy Pulmonary or liver transplant Total cystectomy Adrenal resection Repair of perforated bowel Oesophagectomy

or CAS) Gynaecology: minor Orthopaedic: minor (meniscectomy) Urological: minor (transurethral resection of the prostate)	Neurological or orthopaedic: majör (hip and spine surgery) Urological or gynaecological: major Renal transplant Intra-thoracic: non-major	Liver resection, bile duct surgery Duodeno-pancreatic surgery Aortic and major vascular surgery Open lower limb revascularization or amputation or thromboembolectomy

[1]Copyright from Glance et.al. 2012

In emergency surgical situations, the mortality of the disease outweighs the potential cardiac risk associated with the procedure. In such cases, the aim is to take measures to minimize the possible cardiac adverse outcome. Laparoscopic techniques cause less bleeding, fluid shifts but more intestinal paralysis than open thoracic surgery. It has been advocated in trials that lung functions are less affected (Lestar, M. 2011). In patients with heart failure, symptoms will worsen as it leads to decreased pulmonary venous return. There was no evidence between open surgery and laparoscophy in terms of cardiac risk (Fletcher, G. F. 2001). In non-thoracic surgeries, it is not important whether the surgery is open or laparoscopic when evaluating the preoperative risk status. Endovascular aortic intervention carries less cardiac risk than open surgery (Brown, L.C. 2012). We can save the day with quick treatment for patients. When long-term outcomes are compared, it has little effect on overall survival. Based on this, it should not be forgotten that the type of surgery should be chosen considering the long life expectancy in patients who do not have an emergency (Antoniou, G. A. 2013).

1.2. Functional Capacity

It is measured in the equivalent that is equal to the basal metabolic rate. Sometimes patients do not need to do an exercise test. We can get an idea according to whether or not she/he can do daily activities orally. It shows that the person has a functional capacity of 4 METs to climb two flights of stairs and 7 METs to lift heavy objects. Low functional capacity is especially important in thoracic surgery and interventions. It is not associated with mortality in non-thoracic surgery (Biccard B. M. 2005).

1.3. Risk Indices

In the absence of a patient's urgency, we can assess the risk of death within the first month after clinical risk factors and surgical risks are determined. Lee and NSQIP indices are mostly used. In table 2, the predictors of the Lee index are indicated.

Table 2. LEE index[1]

Risk factors	Points
History of ischemic heart disease	1
High-risk type of surgery	1
History of congestive heart failure	1
Preoperative treatment with insülin	1
Preoperative serum creatine > 2.0 mg/dL	1
History of cerebrovascular disease	1

RISK OF MAJOR CARDIAC EVENT

Point	Class	Risk
0	I	0.4%
1	II	0.9%
2	III	6.6%
3 or more	IV	11%

[1]Copyright from Lee et al.

The Lee index's determination of the risk of a-v heart block and pulmonary edema made it successful compared to other indices (Lee, T. H. 1999).

1.4. Invasive and Non-invasive Tests

It is necessary to know whether the patient has clinical risk factors (table 3). ECG should be performed in all patients over 65 years of age with risk factors and in patients with intermediate or high surgical risk.

Table 3 . Clinical risk factors[1]

Heart failure
Renal dysfunction
Ischaemic heart disease
Stroke or transient ischaemic attack
Diabetes mellitus requiring insülin therapy

[1]Copyright from Lee et al. 1999

Biomarkers should be studied in high-risk patients (Priebe H. J. 2005). The troponin and BNP values studied 48 hours before will help us to evaluate long-term mortality and myocardial injury (Karthikeyan, G. 2009). It is not correct to have routine telecardiography. The aim of non-invasive tests is to detect silent myocardial ischemia, determine valve abnormalities and evaluate ventricular function.

Echocardiography should be performed in patients with clinical risk factors or ECG changes in high-risk surgery. Sometimes test results can guide the type of surgery and anesthesia technique (Halm, E. A. 1996).

The treadmill test can assist in determining functional capacity. It also allows us to predict the ischemic ECG change, heart rate response and

blood pressure change caused by surgical stress (Montalescot, G. 2013).

Pharmacological stress tests may be considered in patients with limited physical capacity. Dobutamine is more preferred than adenosine and dipyridamole. DSE (dobutamine stress test) better predicts the risk of cardiological events in 20-50% of extensive ischemia (Shaw, L. J. 1996). It has a high negative predictive value, but this does not exclude necrosis that will develop postoperatively (Raux, M. 2006). It suggests that the event risk ratio will be high. Like any test, it has its limitations. The test should not be used in severe hypo-hypertension and arrhythmias. It does not affect the outcome of low- and intermediate-risk surgery in patients with stable coronary disease.

Invasive intervention is primarily preferred in patients with acute STEMI. Immediate angiography is required in patients with NSTEMI and unstable chest pain. During the intervention, revascularization should be considered according to the urgency of non-cardiac surgery. In the patient who develops subdural hematoma, it will be more appropriate to intervene with a balloon instead of a stent (Matteau, a. 2012).

2. RISK-REDUCTION STRATEGIES

2.1. Pharmacological

The stress caused by surgery will increase the oxygen demand of the myocardium. The low oxygen offered will trigger ischemia and lead to an increase in heart rate.

Use of beta-blockers reduces mortality in patients considered for high-risk surgery (Shammash, J. B. 2001). Protects from possible myocardial infarction. Beta-blockers that have been used before due to arrhythmia or ischemic heart disease should not be discontinued. Even in the treatment of compensated heart failure, it should not be discontinued before surgery.

In general, the drug dose should be adjusted at the heart rate target of 60-70 beats/min. Bradycardia and hypotension should be avoided. Statins provide plaque stabilization thanks to their pleiotropic effects. It is protective in coronary and peripheral arterial diseases. In one study, a 3-fold higher risk of postoperative death was observed if they were cut in aortic surgery (Le Manach, Y. 2007).

The treatment should be started 2 weeks before the surgery or interventions and should be continued for at least 1 month after the surgery. Although nitroglycerin reduces ischemia, it is not given because it causes hypotension. If beta-blockers are used together with ACE-I and ARB, they should be discontinued 24 hours before due to the risk of severe hypotension. If intermediate-risk surgery is planned

in patients with stable heart failure, there is no need to discontinue the drug.

Non-dihydropyridine derivative calcium channel blockers can only be given as rate reducers in patients who cannot be given beta-blockers.

Caution should be exercised as diuretics will cause electrolyte imbalance and hypovolemia. If there is preoperative heart failure, use should be continued. Clonidine increased the risk of cardiac arrest by causing severe hypotension (Devereaux, P. J. 2014).

2.2. Management of Patients on Anti-platelet Agents

In IHD (ischemic heart disease) patients, withdrawal of aspirin therapy provides a 3-fold increase in the risk of cardiac events. If hemorrhagic complications are thought to develop, treatment may be interrupted. Before spinal and ophtalmological surgery aspirin should be interrupted at least 7 days. These patients can be given a once-daily dose of LMWH.

In patients with stent thrombosis, stent thrombosis results in more adverse outcomes than newly developed coronary ischemia.

In order to minimize bleeding, surgery should be delayed for two weeks after balloon angioplasty, 4 weeks in patients with bare metal stents, and at least 6 months in patients with drug-eluting stents (Wijns, W. 2010).

Clopidogrel and ticagrelor should be discontinued 5 days before the surgical procedure and prasugrel should be discontinued 7 days before.

Patients using vitamin K antagonists should be taken to surgery when INR <1.5. Bridge therapy should be given with LMWH. The last dose should be given 12 hours before surgery (Pengo, V. 2009).

Preoperative medications of patients using NOAC should be discontinued 2-3 times before the half-life of the drug. If the risk of bleeding is high, it can be cut in 4-5 times. The algorithm for bleeding management is presented in figure 1.

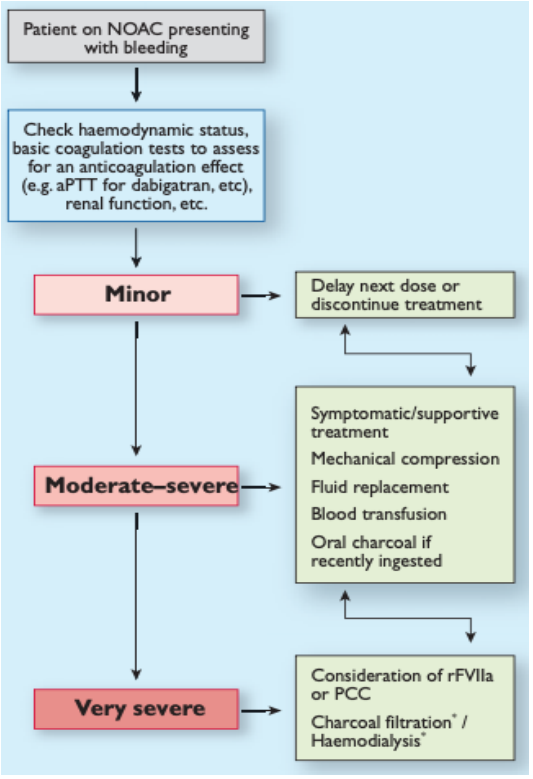

Figure 1. The algorithm for bleeding management of NOAC's[1]

[1] Copyright from Camm et al. 2012

2.3. Revascularization

Stent thrombosis in patients with stent causes more adverse outcomes than newly developed coronary ischemia. In order to minimize bleeding, surgery should be postponed for at least two weeks after balloon angioplasty, at least 4 weeks in patients with bare metal stents, and at least 6 months in patients with drug-eluting stents.

Except for high-risk surgical patients, there is no need for additional evaluation if asymptomatic patients have had CABG within the last 6

years. Prophylactic revascularization should not be considered in stable and asymptomatic patients with coronary artery disease.

3. MANAGEMENT OF ANAESTHETIC

Anesthesia techniques cause decreased sympathetic tone and decreased venous return. The change in mean arterial pressure before surgery and mean pressure during surgery should not be more than 20%. Mean blood pressure below 60 mmHg for more than 30 minutes increases the risk of postoperative cardiac complications (Bijker, J. B. 2012).

Neuraxial techniques reduce postoperative cardiac, pulmonary and thromboembolic complications (Rodgers, A. 2013). Epidural anesthesia has been proven to improve survival. Neuraxial anesthesia involves a low risk of pneumonia (Barbosa, F. T. 2013).

4. SPECIFIC DISEASES

4.1. Chronic Heart Failure

Patients with a systolic ejection fraction less than 35% have a very high risk of developing a postoperative cardiac event (Kazmers, A. 1988). Patients should receive beta-blocker, ACE-i/ARB and diuretic therapy. If hypotension is thought to develop, ACE-i/ARB should be discontinued one day in advance. Cardiac resynchronization can be implanted in patients with low ejection fraction and QRS>120 ms (McMurray, J. J. 2012). Surgery should be postponed for three months in patients with acute heart failure. The aim here is to allow the

ventricle to remodel (Upshaw, J. 2013). In heart failure with preserved ejection fraction, diuretic therapy is required to prevent volume overload.

4.2. Arterial Hypertension

Sympathetic activation begins with the induction of anesthesia, and heart rate increases with blood pressure. In general, the increase in heart rate is around 15-20 beats. The increase in blood pressure is between 20-30 mmHG. This increase is higher in individuals with chronic hypertension. Surgery should be postponed and preoperative medical treatments must be arranged. Surgery is not required to be delayed in stage 1 or 2 hypertensive patients.

4.3. Valvular heart disease

Rhythm and volume changes may be symptomatic in patients with aortic valve stenosis. Before elective surgery, the valve area should be evaluated and if necessary, transcatheter valve implantation or valve replacement should be performed.

Patients with mitral valve stenosis are at risk of developing atrial fibrillation. Excessive volume should be avoided. Patients with asymptomatic pulmonary artery pressure >50mmHg should undergo a percutaneous mitral commissurotomy (Vahanian, A. 2012).

As long as the ejection fraction does not decrease in valve regurgitations, low and intermediate risk surgery can be performed safely.

In patients with prosthetic valves, preoperative anticoagulants can be discontinued and replaced with therapeutic doses of LMWH or UFH. İntermediate and high-risk patients with valve disease who will undergo elective surgery should be evaluated with echocardiography.

4.4. Arrhythmias

Preoperative catheter ablation should be performed in patients with WPW (Wolff-Parkinson-White) in electrocardiographic examination and in patients with paroxysmal AF attacks. Carotid artery imaging is required in patients who have TIA due to atrial fibrillation. Carotid artery revascularization should be considered if a TIA has been experienced in the last 6 months.

Monomorphic VT is associated with scarring, while polymorphic VT is associated with ischemia. Beta-blocker has been proven to reduce and prevent arrhythmia (Balser, J. R. 1998).

A temporary pacemaker can be inserted in patients with symptomatic asystole or complete a-v block. Since the devices of patients with permanent pacemakers are affected by electrocautery, the pacemaker should be turned off during surgery.

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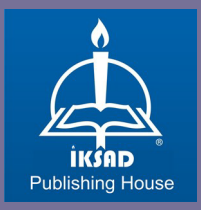

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