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DIC

Disseminated intravascular coagulation (DIC) is a state of hemostatic dysregulation which causes microvascular clotting and consumptive coagulopathy and is seen in a variety of conditions including sepsis (most common), trauma, malignancy, liver diseases, and toxins. These conditions can cause cytokine-induced endothelial and mononuclear cell release of tissue factors and generation of excessive thrombin extending outside the local area of injury along with release of fibrinolytic proteins. Excessive thrombi production leads to microvascular thrombi with consumption of platelets, procoagulant and anticoagulants proteins, and inhibition of fibrinolysis. All these factors contribute to multiorgan failure. Diagnosing DIC is difficult since it includes a wide range of clinical presentations, including mild to excessive bleeding and systemic thromboembolic phenomenon associated with multiorgan failure. The International Society on Thrombosis and Hemostasis (ISTH) diagnostic scoring system for overt DIC is widely utilized in intensive care units for diagnosing DIC, including sequential testing of components of the ISTH scoring system such as prothrombin time, platelet count, fibrinogen, and D-dimer. Fibrinogen does not seem to have a significant impact on the prediction of DIC. Among individual DIC components evaluated, prolonged PT is the most predictive of increased vasopressor use, followed by elevated D-dimer. Pediatric patients presenting with suspected sepsis to the emergency department who have scores greater than three are more likely to have outcomes including increased vasopressor use, increase mortality, prolonged hospital and intensive care unit lengths of stay, increased rates of mechanical ventilation, and increase mortality. The predominant condition leading to DIC is sepsis affecting 75,000 children per year in the USA with mortality rates ranging between 7010% among all age groups. Sepsis is a syndrome with a variety of clinical manifestations including organ dysfunction caused by a dysregulated host response to the inciting infection. Septic shock produces profound circulatory, cellular, and metabolic abnormalities associated with high-risk morbidity and mortality. Coagulation activation can be triggered with septic shock leading to activation and inhibition of physiological anticoagulation mechanisms and fibrinolytic system leading to intravascular fibrin formation and consumption of procoagulant leading to DIC. DIC then results in hemorrhage or thrombotic occlusion of vessels leading to inadequate blood and oxygen to various organs leading to multiple organ dysfunction syndrome. DIC results from the acceleration of the clotting cascade, inactivation of endogenous anticoagulants, and modification of fibrinolysis, leading to hypercoagulability and augmented fibrinolysis. This event causes the formation of multiple microthrombi in the systemic circulation, which consequently manifests as multiorgan failure. The main management of DIC is early identification and treatment of the underlying condition, hemodynamic support, frequent

monitoring of laboratory and clinical parameters, and replacement of consumed coagulation factors and blood components via transfusion of platelets, fresh frozen plasma, or cryoprecipitate. Prophylactic transfusion of these blood products is not recommended unless there is clinical bleeding or impending invasive procedure (surgery). There is a demonstrated efficacy of antithrombin and protein C concentrates, recombinant activated protein and recombinant thrombomodulin for the management of DIC in children. Activated protein C inactivates coagulation factors V and VIII, and ultimately causes inhibition of thrombin formation and has anti-inflammatory properties. Recombinant thrombomodulin activates protein C leading to the inactivation of factor Va, which ultimately leads to the inhibition of thrombin generation.

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Extracolonic Manifestations of FAP

Familial adenomatous polyposis (FAP) is a hereditary syndrome of autosomal dominant inheritance caused by a germline mutation in the adenomatous polyposis coli (APC) tumor suppressor gene in the long arm of chromosome 5 characterized by 100-1000 adenomatous polyps in the colon and rectum with progression to cancer if left untreated. The less aggressive variant termed attenuated FAP exhibits fewer colorectal adenomatous polyps (10-100), later age of adenoma appearance and a lower cancer risk. FAP accounts for 1% of all colorectal cancers in the USA. Many of these hereditary syndromes have extracolonic manifestations, including the development of benign and malignant tumors. These extracolonic manifestations can be the first sign of the inherited syndrome helping establish an early diagnosis of FAP in high-risk patients who have not yet developed colorectal polyposis. Extracolonic cancer in FAP has become of significant concern since affected patients are living longer and are increasingly being diagnosed earlier. The majority of FAP patients (over 70%) present with some level of extracolonic manifestation during the course of the disease. Extracolonic manifestation can be classified according to the tissue of origin into ectodermal, endodermal, and mesodermal. Ectodermal lesions include epidermoid or sebaceous cysts which occur with increasing frequency at a younger age with predilection in the face, scalp, legs, and arms. Also, congenital hypertrophy of the retinal pigment is a well-recognized ocular sign and clinical marker occurring in more than

90% of FAP patients. Ocular lesions are discrete, darkly pigmented, round, oval or kidney shape raging in size from 0.1-1.0 optic disk diameter. Lesions of mesodermal origin include desmoid disease, lipomas, fibromas, osteomas, and dental abnormalities such as odontomas, dentigerous cysts and supernumerary teeth. Dentists should consider referral of patients with extranumerary teeth or jaw osteomas for FAP evaluation. Desmoid tumors are slow growing mesenchymal neoplasms composed of fibroblasts and myofibroblasts within a rich collagen matrix. Desmoid tumors are most commonly (80%) intraabdominal (mesentery of retroperitoneum). Other sites include abdominal wall, subcutaneous, and in the musculo-aponeurotic layer. They can reach massive size, cause intestinal obstruction, mesenteric vascular obstruction, and ureteric obstruction. They lack a metastatic potential but exhibit aggressive local behavior with infiltrative patterns of growth involving surrounding structures and a high local recurrence rate following resection. Desmoid tumor development can be exacerbated by surgical trauma or pregnancy. The frequency of developing desmoid tumors is higher for FAP with a lifetime risk of 8% for males and 15% for females. Management of desmoid tumors is complex and depends on location, symptoms, extent of disease and pattern of growth. Radiation therapy, NSAID's, antiestrogen and chemotherapeutic are options. Surgery is used for those unresponsive to medical treatment or if complications requiring emergency surgery occur. Recently, Imatinib has been shown to positively impact progression-free survival in patients with advance desmoids. Osteomas may occur in the mandible, maxilla, sinuses or calvarium of the skull. Exostosis may be found in the skull, digits, and long bones. Lesions of endodermal origin include gastrointestinal adenomas and carcinomas. After the colon and rectum, the duodenum is the second most common site of polyp development in patients with FAP. Non-adenomatous fundic gland polyps predominate in the stomach, while duodenal lesions were mostly adenomatous in nature. The most common extracolonic manifestations with FAP are upper gastrointestinal polyps, including gastroduodenal adenomas that can progress to cancer. Upper GI polyps in the setting of FAP are located in the stomach, duodenum and periampullary region. Gastric polyps are typically non-adenomatous benign fundic gland polyps considered hamartomas. They develop in almost 50% of FAP patients, are located in the antrum, and are not associated with cancer. Duodenal adenomatous polyps in FAP are found in 30-70% of individuals, have a predilection for the second and third portion of the duodenum, have a strong propensity toward developing into duodenal cancer and a genotypic/phenotypic correlation with mutation in exon 15 of the APC gene has been described. Duodenal cancer is the second most common cause of disease-related mortality in patients with FAP with a lifetime risk of approximately 3-5%. Is one of the leading causes of death in patients who have undergone prophylactic colectomy. Increasing age appears to be correlated with higher risk of progression to advanced polyposis. Endoscopic surveillance is recommended starting between age 25 and 30 or 5 years earlier than any affected family member with duodenal adenomatous polyps. The Spigelman classification is used to evaluate polyp severity based on number, size, histology, and presence of dysplasia. Management of duodenal polyps consists of pharmacologic (non-steroidal inflammatory drugs) which has been found ambiguous, endoscopic, or surgical removal. Among FAP patients the risk of death is higher than in the general population (3-fold); disease related mortality is caused more commonly by upper gastrointestinal malignancies followed by desmoid tumors and perioperative complications.

Other less common extraintestinal malignancies associated with FAP include thyroid, brain (medulloblastoma), adrenal, hepatoblastoma and pancreatobiliary tumors. Thyroid cancer is the third most common malignancy associated with FAP. Is most commonly papillary histology, presents in the second or third decades of life, mostly in females. The cribriform-morular histologic variant of papillary thyroid cancer is highly suggestive of FAP. Periodic thyroid ultrasound screening should be considered in patients with FAP, and FNA in those with thyroid nodules. The risk of pancreatic adenocarcinoma is also increased in patients with FAP. Mutations in the APC gene are associated with several other extraintestinal manifestations including Turcot and Gardner syndromes. Gardner's syndrome is characterized by the typical manifestations of FAP and presence of osteomas, fibromas, and epidermoid cysts.

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Delayed Separation Umbilical Cord

The umbilical cord connects the fetus to the placenta in the uterus, is made of blood vessels (two arteries and one vein), and connective tissue. The umbilical cord of newborn infants separates during the first two weeks of life, though there is a wide variation in the time this event takes place with regard to ethnicity, geographical location and proper care of the cord. The mean umbilical separation time is 6.6 days, with a median of seven days. The cord stump dries and falls off, and the wound heals. The cord separation is mediated by leukocytes. Histologically this process is characterized by granulocyte influx and phagocytosis at the base of the cord. Delayed separation of the umbilical cord is defined as separation that occurs after three weeks of life. Factors associated with delayed separation of the cord include the use of alcohol or chlorhexidine for cleaning purpose, prematurity, and infants born by cesarean section. Neonates delivered by cesarean section tend to have longer cord separation time due to less bacterial colonization after birth. The use of postpartum antibiotics, parenteral nutrition and phototherapy also delayed the separation of the umbilical cord. Sepsis delays the cord separation time by sixfold beyond the second week of life. Urachal anomalies rarely can be associated with delayed separation. According to the National Institute of Health Care and Excellence guidelines, parents should be advised how to keep the umbilical cord clean and dry, and that antiseptics should

not be used routinely. A marked delayed in umbilical cord separation raises the suspicion of leukocyte adhesion deficiency (LAD), a rare autosomal recessive hereditary disorder leading to defective neutrophil function. LAD is a disorder of neutrophils due to a genetic defect in the beta subunit of the integrin molecule ITGB2 which encodes the integrin beta chain-2 protein CD18. This defect leads to dysfunction of leukocyte adhesion to the wall of blood vessels and migration of leukocytes to sites of infection and inflammation. Patients have a complete absence of neutrophils at the site of inflammation causing recurrent bacterial infections and sepsis. LAD is characterized by recurrent infections, impaired pus formation, delayed wound healing, omphalitis, and delayed separation of the umbilical cord as hallmark features of the disease. Patients are infected with common pathogenic agents but not opportunistic ones and respond well to antimicrobial therapy. Proteus, Klebsiella, Staphylococcus aureus, Pseudomonas aeruginosa, and enterococci are the most common pathogens affecting LAD patients. The severe form of this disease remains a life-threatening condition with limited 2-years survival in the absence of transplantation. The flow cytometric analysis of monocytic intracellular tumor necrosis factor-alpha production in response to lipopolysaccharide may be a useful method to screen for the disease. Management of LAD consists of allogeneic stem cell or bone marrow transplantation.

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