Current Approaches in Child Health and Diseases

Editor
Fatma YILMAZ KURT

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PREFACE

"Nations whose children are not raised in a healthy and conscious manner collapse as quickly as buildings with a rotten foundation."

Mustafa Kemal ATATÜRK

Among the various demographic indicators that indicate a country's level of development, the childhood mortality rate is the most significant. To decrease child mortality rates, it is crucial to implement preventive measures for diseases, stay up-to-date with advancements in treatment, and follow the appropriate approach in this direction. This book covers current approaches to certain diagnoses in the field of Pediatrics. The main objective is to offer current information that students and colleagues can use in the clinical setting for the improvement, protection, prevention, treatment, and care of children's health. Additionally, this book aims to expand the written resources available on Pediatrics and create a fundamental resource in interdisciplinary fields.

I would like to express my gratitude to all the authors who dedicated their time and effort to the development of this book with great dedication and effort in the middle of their busy work. Additionally, I extend my gratitude to the staff of BIDGE Publications for their contributions to the printing and typesetting of the book.

It is my hope that this book will serve as a valuable resource for our colleagues.

Sincerely,

Editor

Assoc. Prof. Dr. Fatma YILMAZ KURT

Contents

CHAPTER I

Necrotizing Enterocolitis In Newborn Babies and Its Surgical Treatment

Mehmet UYSAL[1]

Introduction

Necrotizing enterocolitis (NEC) is a gastrointestinal system problem characterized by partial or complete ischemia of the intestines. This disease was first described in the 19th century and the terminal ileum is often involved. The reasons for the initiating factors in the occurrence of intestinal ischemia have not been fully elucidated; However, the end point it causes is intestinal ischemia (Neu J, 1996). Necrotizing enterocolitis (NEC) is one of the diseases detected in newborns and can cause the most serious gastrointestinal problems. It occurs in 3-15% of neonatal intensive care units, and

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more than 90% of those affected are babies born before the 32nd week of gestation. According to the research results of the Turkish Neonatology Association, this rate is 9.1% in babies with very low birth weight (VLBW) (Kosloske AM, 1994). There was no desired reduction in mortality and morbidity rates related to NEC. The main reason for this is the increase in the rate of infants with reduced mortality. Although most newborn babies with necrotizing enterocolitis are premature, approximately 13% of the cases are full-term babies (Horbar JD, Badger GJ, Carpenter JH, et al, 2002), and most full-term babies with NEC have an underlying disease (Sankaran K, Puckett B, Lee DS, et al, 2004).

In a clinical study, the underlying cause was identified in 16 of 26 full-term NEC cases. Of these cases; Congenital heart disease was detected in six patients, sepsis, hypoglycemia, seizure, severe intrauterine growth retardation, hypercoagulability, gastroschisis and congenital herpes infection were detected in 10 patients (Lee SK, McMillan DD, Ohlsson A, et al, 2000). In another clinical study at a regional center, it was determined that 30 of the babies older than 36 weeks who were diagnosed with NEC between 2001 and 2006 had a predisposing disease. It is stated that these are congenital heart disease, respiratory distress, sepsis, anoxic birth and polycythemia, according to the frequency of detection, and that the nutrition method of none of these patients is only breast milk (Schanler RJ, 2015). In the case series consisting of 39 babies with a gestational age over 37 weeks between 1990 and 2012, some prenatal factors such as maternal substance use, intrapartum infection, maternal diabetes, and pregnancy-induced hypertension were detected in 15 babies. It was determined that two-thirds of the cases involved perinatal and neonatal diseases such as infection, hypoxic state, congenital heart disease and genetic anomalies, and the mortality rate was 18% (Ostlie DJ, Spilde TL, St Peter SD, et al, 2003).

Necrotizing enterocolitis occurs due to nutritional deficiency in the intestines. Clinical and laboratory findings of this disease vary depending on the course of NEC and the pathological factors that predispose to the disease. Although the terminal ileum and colon are

generally affected in NEC patients, the entire gastrointestinal system may be affected in delayed cases. (Lambert DK, Christensen RD, Henry E, et al, 2007). In NEC, the intestines are macroscopically edematous and hemorrhagic. In the intestines, subserosal gas may occur along the longitudinal mesentery and gangrenous necrosis and perforation may occur in the antimesenteric area. As the intestines renew themselves, their walls become thinner, fibrinous adhesions and strictures form. Edema, bleeding and full-thickness necrosis after mucosal damage are the most common histological consequences of NEC. Other findings include the emergence of bacteria and gas along the intestinal wall secondary to inflammation. Vein thrombus is not common in this type of cases (Short SS, Papillon S, Berel D, et al, 2014).

While the pathogenesis of necrotizing enterocolitis may be idiopathic, it is a disease caused by one or more etiological factors and may cause mucosal injury. It is thought that prematurity, excessive increase in microbial agents, nutrition, impaired intestinal circulation and mucosal integrity, polymicrobial overgrowth, and drugs that cause deterioration of intestinal mucosal integrity play a role in the pathogenesis. In recent epidemiological clinical studies, prematurity and have been identified as important risk factors for NEC (Kliegman RM, Walker WA, Yolken RH, 1993).

Immaturity of the gastrointestinal system and immune system prepares the ground for NEC in preterm babies. The immature mucosal barrier allows bacterial translocation to a greater extent than at term, with increased permeability. Immature local host defense mechanisms, decreased concentrations of secretory immunoglobulin A, mucosal enzymes (such as pepsin and protease) and other protective agents (such as lactoferrin), and increased gastric pH contributing to bacterial proliferation predispose to NEC. Small intestinal motility is reduced in premature babies, therefore transit time is prolonged and bacterial proliferation and overgrowth are increased (Holman RC, Stoll BJ, Clarke MJ, Glass RI, 1997).

Bacterial proliferation and increased intestinal permeability are two factors that contribute to the inflammatory response resulting from the translocation of bacteria from the intestinal lumen to the intestinal wall and the activation of cytokines. Administration of glucocorticoids matures intestinal barrier function, and prenatal administration is recommended in premature infants to reduce the incidence of NEC. In term babies, NEC is more likely to be associated with underlying predisposing conditions (Morriss FH Jr, Moore M, Gibson T, West MS, 1990). More than 90% of infants with necrotizing enterocolitis were fed. Enteral nutrition may be effective in the formation of NEC because it provides a substrate for bacterial proliferation in the intestine. However, NEC has also been detected in babies who were not fed at all. In newborns, especially premature babies, the digestive and absorption functions of nutrients are not fully developed. Some agents formed by bacterial fermentation of incompletely digested carbohydrates and lipids in the intestine result in mucosal damage or injury, and are exacerbated by impaired intestinal peristalsis and delayed progression time. In an animal experimental study, casein, organic acids, and low pH were found to result in mucosal damage and injury through infiltration of cellular elements and vasoactive compounds (Bauer CR, Morrison JC, Poole WK, et al, 1984).

Although enteral nutrition is related to NEC, the effect of nutritional agents on the formation of NEC is not very clear. In a clinical study conducted in 2011, it was determined that gradually increasing nutrition did not reduce the likelihood of NEC formation, but was accompanied by a delay in regaining birth weight and transition to full enteral nutrition (Halac E, Halac J, Bégué EF, et al., 1990). Small amounts of enteral or trophic nutrition do not increase the degree of occurrence of NEC (Clark DA, Miller MJ, 1990). Delaying enteral feeding leads to atrophy of the intestinal mucosa and a decrease in the concentrations of gastrointestinal enzymes that ensure the maturation of intestinal motor activity. It is recommended that premature babies be fed enterally with a small amount of breast milk from birth. It has been shown that trophic nutrition does not

increase the incidence of NEC, even in patients with umbilical artery catheters (Morgan J, Young L, McGuire W, 2011)

Breast milk is more protective against NEC in premature babies compared to formula. Factors that reduce inflammation in breast milk or present foreign antigens to the gastrointestinal tract may play a role in this protection. Breastfeeding facilitates the proliferation of non-pathogenic bacteria that fight pathogenic bacteria by providing low intestinal pH. The intestinal mucus covering is less affected by breast milk, and growth factors in breast milk (such as epidermal growth factor) repair damage to the barrier. Breast milk increases intestinal motility and also activates the mucosal defense system. Substances that prevent the formation of NEC in breast milk; platelet activating factor, acetylhydrolase, secretory immunoglobulin A (Ig A), cytokines such as interleukin 10, interleukin 11, epidermal growth factors, nucleotides, antioxidants such as glutamine and vitamin E, carotene and glutathione. (Morgan J, Young L, McGuire W, 2014).

Since intrauterine NEC does not occur while the baby is in the womb, bacterial proliferation is thought to have a significant effect on the formation of NEC. After birth, bacteria proliferate in the intestines under the influence of the mother's recto-vaginal flora. These bacteria play an integral role in the expression of intestinal toll-like receptors and genes involved in intestinal physiology, postnatal maturation and function (barrier, digestion, angiogenesis and Ig A production), and protection against pathological microorganisms (La Gamma EF, Browne LE, 1994). Pathological host-bacteria interaction can induce pro-inflammatory and pro-apoptotic responses in intestinal host cell-mediated signaling pathways such as the NF-kappa B pathway (Schanler RJ, Shulman RJ, Lau C, et al, 1999, Bombell S, McGuire W, 2009).

Although the role of bacteria in prenatal and postnatal intestinal development is not clear, overgrowth of intestinal non-commensal bacteria, especially coagulase-negative staphylococci, seems to be related to NEC (Hunter CJ, Upperman JS, Ford HR,

Camerini V 2008). This overgrowth can affect intestinal maturation, increase inflammation and apoptosis, and also induce mucosal damage by endotoxin secretion. This condition can also be seen without primary infection and may play a role in the disease process (Hooper LV, Wong MH, Thelin A, et al, 2001). Approximately 20-30% of babies with necrotizing enterocolitis have bacteremia and the causative agent is usually coagulase-negative staphylococcus. It is usually caused by passage through damaged intestinal mucosa (Patel RM, Denning PW, 2015).

Necrotizing enterocolitis can also occur with primary intestinal invasion by pathogenic enteric bacteria. Some bacteria, usually more distal to the gastrointestinal tract (Escherichiacoli, Klebsiela pneumonia, and Clostridium difficile), have been identified in the blood and peritoneal cavity of infants with NEC (Stewart CJ, Marrs EC, Magorrian S, et al, 2012). In some sporadic and epidemic cases, viral and fungal pathogens, as well as bacteria, have been detected. (Jacquot A, Neveu D, Aujoulat F, et al, 2011). In a small prospective study in which 12 premature babies with a gestational age of less than 34 weeks were included, the feces of the babies were examined using polymerase chain reaction and gel electrophoresis and three of the babies survived. Clostridium perfringes was detected in the first week of life and NEC developed in these babies in the following period, but NEC development was not observed in nine babies who were not detected (Alexander VN, Northrup V, Bizzarro MJ, 2011).

Damaged or injured mucosal barriers cause bacteria to invade deeper tissues and inflammation to progress. The mucosal barrier in the intestines has many components; Among these, some provide physical barriers, while others provide biochemical and immunological barriers. Factors that aid innate immunity are intestinal lumen pH, enzymes, mucin, epithelial barriers, intestinal peristalsis, and non-specific antimicrobial agents such as lactoferrin and lysozyme. In premature babies, these agents are not yet developed, and their levels in the intestinal lumen are even lower than in term babies (Cotten CM, Taylor S, Stoll B, et al, 2009).

Although enteral nutrition is associated with NEC, the importance of nutrition-related factors in the development of NEC is not clear. In a review published in 2011, it was stated that slowly increasing nutrition did not reduce the risk of NEC, but caused a delay in regaining birth weight and transition to full enteral nutrition (Stuart RL, Tan K, Mahar JE, et al, 2010). A meta-analysis showed that delaying enteral nutrition (more than four days) did not reduce the risk of NEC and caused a delay in the time to switch to full enteral nutrition. Minimal enteral or trophic nutrition does not increase the incidence of NEC (Lin PW, Stoll BJ, 2006). Delaying enteral feeding leads to atrophy of the intestinal mucosa and a decrease in the concentrations of gastrointestinal enzymes that ensure the maturation of intestinal motor activity. It is recommended that premature babies be fed enterally with a small amount of breast milk from birth. It has been shown that trophic nutrition does not increase the incidence of NEC, even in patients with umbilical artery catheters (Warner BB, Ryan AL, Seeger K, et al, 2007).

In premature babies, breast milk is more protective against NEC compared to formula. Factors in breast milk that reduce inflammation or present foreign antigens to the gastrointestinal tract may be effective against NEC. Breastfeeding is effective by maintaining a low intestinal pH, increasing non-pathogenic bacteria that fight pathogenic bacteria. The intestinal mucus lining is less affected by breast milk, and growth factors in breast milk (such as epidermal growth factor) repair the injury to the barrier. Breast milk increases intestinal motility and also stimulates the mucosal defense system. Preservatives in breast milk; platelet activating factor, acetylhydrolase, secretory immunoglobulin A (Ig A), cytokines such as interleukin 10, interleukin 11, epidermal growth factors, nucleotides, antioxidants such as glutamine and vitamin E, carotene and glutathione (Schanler RJ, 2016).

Bacterial colonization is believed to have a very important role in the development of NEC because NEC does not occur in the womb when the intestines are sterile. After birth, colonization of the intestinal tract with maternal rectovaginal flora bacteria occurs.

These bacteria play a symbiotic role in the expression of intestinal toll-like receptors and genes involved in intestinal physiology, postnatal maturation and function (barrier, digestion, angiogenesis and Ig A production), and protection against pathological microorganism. Pathological host-bacteria interaction can induce pro-inflammatory and pro-apoptotic responses in intestinal host cell-mediated signaling pathways such as the NF-kappa B pathway (Mohamed A, Shah PS, 2012).

Although the role of bacteria in prenatal and postnatal intestinal development is not clear, non-intestinal commensal bacteria, especially coagulase-negative staphylococci, may induce pro-inflammatory and pro-apoptotic responses. Its excessive proliferation seems to be related to NEC. This overgrowth can affect intestinal maturation, increase inflammation and apoptosis, and also induce mucosal damage by endotoxin secretion. This condition can also be seen without primary infection and may play a role in the disease process. Approximately 20-30% of babies with necrotizing enterocolitis have bacteremia and the causative agent is usually coagulase-negative staphylococcus. It is usually caused by passage through damaged intestinal mucosa (Stritzke AI, Smyth J, Synnes A, et al, 2013).

Necrotizing enterocolitis may also occur with primary intestinal invasion of pathogenic enteric bacteria. Some bacteria (Escherichiacoli, Klebsiela pneumonia and Clostridium difficile), which are usually found in the distal gastrointestinal tract, have been detected in the blood and peritoneal cavity of patients with NEC (Keir AK, Wilkinson D, 2013). In addition to bacteria, viral and fungal pathogens have also been isolated in some sporadic cases and epidemic outbreaks (Guillet R, Stoll BJ, Cotten CM, et al, 2006). In a small prospective study in which 12 premature babies with a gestational age of less than 34 weeks were included, the feces of the babies were examined using polymerase chain reaction and gel electrophoresis and three of the babies survived. Clostridium perfringes was detected in the first week of life and NEC developed in these babies in the following period, but NEC development was

not observed in nine babies who were not detected (Rao SC, Basani L, Simmer K, et al, 2011).

Disrupted mucosal barriers allow bacteria to migrate into deeper tissues and ultimately cause inflammation. The mucosal defense in the intestines has many components, some of which provide a physical barrier and some provide a biochemical and immunological barrier. Factors that contribute to innate immunity are luminal pH, enzymes, mucin, epithelial barriers, intestinal motility and nonspecific antimicrobial factors such as lactoferrin and lysozyme. In premature babies, these factors are more immature and their levels are lower than in term babies (Kliegman RM, Walker WA, Yolken RH, 1993).

Secretory IgA is the major gastrointestinal protective antibody and is not found in the intestines at birth. The number of Paneth cells that secrete lysozyme, phospholipase A2 and antimicrobial peptides is less in premature babies than in term babies. The intestinal mucin barrier is immature in premature babies, therefore the penetration and adherence of bacteria is impaired. has increased. This may cause mucosal damage or result in inflammation (Bombell S, McGuire W, 2009).

Growth factors such as epidermal growth factor (EGF) are important in intestinal development and maintenance of barrier function. In a study conducted on babies with a gestational age of less than 32 weeks, it was found that the salivary EGF levels of babies who developed NEC were lower than those who did not develop NEC, but new studies are needed to determine the role of EGF in predicting or protecting from NEC (Warner BB, Ryan AL, Seeger K et al, 2007).

Ischemic conditions of the gastrointestinal tract are thought to be one of the most important factors contributing to the formation of NEC, but most babies with NEC do not have a perinatal hypoxic ischemic state. Circulatory disorders that play a role in the development of necrotizing enterocolitis are perinatal asphyxia, recurrent apnea, and severe respiratory distress syndrome. hypoxia,

hypotension, congenital heart disease, patent ductus arteriosus, heart failure, umbilical artery catheterization, anemia, polycythemia, erythrocyte transfusion and blood exchange. However, most of these conditions are seen in term babies. The role of circulatory dysfunction in the development of NEC in preterm infants is unclear. Based on these findings, it has been hypothesized that a slight decrease in blood flow or subsequent reperfusion in response to hypoxia may cause intestinal damage (Cotten CM, Taylor S, Stoll B, et al, 2009, Schanler RJ, 2016).

Many studies have reported a relationship between erythrocyte transfusion and NEC. In a study of 11 case-control and one cohort study, it was reported that patients thought to have transfusion-related NEC had lower birth weights than those without transfusion-related NEC, and were probably more likely to have patent ductus arteriosus or receive ventilator support. The authors point out that the risk of mortality is higher in babies thought to have transfusion-related NEC, but these results do not prove a cause-effect relationship between NEC and erythrocyte transfusion (Mohamed A, Shah PS, 2012). Similar findings were found in a case group of 927 preterm babies with NEC conducted in Canada and It was also found in the study in which 2781 preterm babies without NEC were taken as the control group. In this study, the rate of receiving transfusion in the past two days was found to be higher in the NEC group. In this study, it was found that babies who developed NEC within two days after transfusion had a lower gestational age and higher disease scores than the control group and babies who developed NEC not related to transfusion (Stritzke AI, Smyth J, Synnes A, et al, 2013). It has been suggested that stopping feeding during transfusion may reduce the risk of NEC, but this practice does not affect the prevalence of NEC. Data regarding its effects are not sufficient (Keir AK, Wilkinson D, 2013).

The use of hyperosmolar medications or formulas may cause mucosal damage and the development of NEC. Oral medications such as theophylline, multivitamins and phenobarbital contain hypertonic additives and may irritate the intestinal mucosa. Foods

with recommended boosters added or concentrated with multiple additives should also be avoided in the first few weeks of life. Histamine type 2 receptor antagonists (H2 antagonists), such as ranitidine and cimetidine, have also been associated with the development of NEC. This relationship was demonstrated in a study published by the NICHHD Neonatal Research Network. In a study conducted with 11072 babies with birth weights ranging from 400 g to 1500 g, it was observed that the rate of taking H2 antagonists was higher in patients with NEC (Schanler RJ, 2016, Guillet R, Stoll BJ, Cotten CM, et al, 2006).

Inflammatory cytokines induced by ischemia, infectious agents, or mucosal irritants can increase mucosal damage. Inflammatory cytokines such as tumor necrosis factor (TNF), interleukins (IL-1, IL-6, IL-8, IL-10, IL-12 and IL-18) and platelet activating factor (PAF) increase vascular permeability and inhibit inflammatory cells. pulls. The levels of these cytokines increased in premature infants with NEC, correlating with the severity of the disease. Drugs or conditions that affect the formation of cytokines or free oxygen radicals may also contribute to the development of NEC. Chorioamnionitis is an antenatal proinflammatory process involving the placenta and fetal membrane and may contribute to the pathogenesis of NEC. However, the data regarding whether it is a clinical risk factor is not clear (Schanler RJ, 2016).

Surgical treatment

When necrotizing enterocolitis is diagnosed or suspected, pediatric surgery consultation should be performed to evaluate the baby, help with the management of the treatment, and schedule surgery. In these babies, surgery is required when necrosis spreads to the intestinal wall and perforation occurs. In the presence of pneumoperitoneum on abdominal radiography, the decision for surgery should be made. However; Peritonitis, severe necrosis or perforation may not be evident on radiography with free air. In conclusion; Other findings supporting peritonitis, such as gradual deterioration in clinical condition, presence of an abdominal mass,

ascites or intestinal obstruction, should be evaluated (Rao SC, Basani L, Simmer K, et al, 2011).

Surgical procedures applied; It involves resection of the affected bowel area with exploratory laparomia or primary peritoneal drainage (PPD). Although laparotomy is more common, it is not clear which procedure is more effective. Based on limited data, it can be said that peritoneal drainage is an alternative method to laparotomy. Especially PPD may be the initially preferred surgical procedure in babies with LBW (advanced low birth weight less than 1000 g). Because it can be performed at the bedside with local anesthesia. In laparotomy, the patient is usually transported to the operating room and general anesthesia is required. It may also require a second surgical intervention for reanastomosis (Tepas JJ 3rd, Sharma R, Leaphart CL, et al, 2010).

Complications

Acute complications:

These can be classified as follows:

*Infectious complications: meningitis, peritonitis or abscess formation, sepsis.

*Disseminated intravascular clotting that causes bleeding in the intestines and other organs.

*Respiratory and circulatory system related hypotension, shock and respiratory failure.

*Metabolic complications such as hypoglycemia and metabolic acidosis.

(Duro D, Kalish LA, Johnston P, et al, 2015).

Late complications:

The most common late complications in the follow-up of necrotizing enterocolitis are stenosis secondary to stricture in the

intestine and short bowel syndrome, which includes surgical intervention (Schanler RJ, 2015).

Stricture formation: This condition is an indication for surgical resection. Intestinal strictures occur in 9-36% of medically or surgically treated infants and are unrelated to the severity of NEC, the presence of pneumatosis intestinalis, or gestational age. Although even the ileum and jejunum can be affected, most of the strictures occur in the colon. Stenosis tends to occur in multiple regions and typically develops 2-3 weeks after the acute episode, but can sometimes be detected 20 months later. Recurrent infections, bloody stools, growth retardation and intestinal obstruction in patients who develop intestinal stenosis. Contrast enemas are used to detect intestinal narrowing or strictures 4-6 weeks after the acute phase of NEC or when feeding intolerance develops, before enterostomy closure and reanastomosis Short bowel syndrome develops in 9% of babies who have undergone surgery for NEC. It results in severe malabsorption (Schanler RJ, 2015). Necrotizing enterocolitis is the most common cause of neonatal-onset intestinal failure after congenital intestinal defects. These babies are at risk for sepsis, cholestasis, and liver failure due to long-term administration of TPN. Intestinal and hepatic transplantation is lifesaving in patients with these complications. In a multicenter prospective study, it was shown that the risk of short bowel syndrome in babies after NEC surgery increases in the presence of the following factors (Duro D, Kalish LA, Johnston P, et al, 2010).

*Parenteral antibiotic therapy should have been started when necrotizing enterocolitis was diagnosed.

*Body weight below 750 grams at birth

*Mechanical ventilation should be followed when necrotizing enterocolitis is diagnosed.

*Enteral nutrition before necrotizing enterocolitis is diagnosed.

Based on the actual percentage of resected short bowel, there are confusing results regarding short bowel resection, the presence of jejunostomy, and its duration of use. Other rare complications of necrotizing enterocolitis are enterocele, enterocolic fistula, and intra-abdominal abscess (Duro D, Kalish LA, Johnston P, et al, 2010).

Spontaneous intestinal perforation (SIP) of the newborn is an isolated perforation and typically occurs in the terminal ileum. Similar to NEC, it is seen primarily in VLBW and IDDA babies. However, it is a different entity from NEC and is the most serious gastrointestinal complication of premature babies. The risk is 2-3% in VLBW babies and approximately 5% in LBW babies. The average gestational age of occurrence is 25-27 weeks and the average body weight is 670-973 grams. It is more common in boys than girls (Kim E MD, Brandt M MD).

Prematurity is the only known definitive risk factor for SIP. Severe chorioamnionitis in the antenatal period is also reported as a risk factor. In a case-control study of sixteen premature babies, more severe chorioamnionitis (40% vs. 12%) was detected in patients with SIP compared to the control group, and it was determined that the mothers of babies with SIP received more antibiotics before birth (Ragouilliaux CJ, Keeney SE, Hawkins HK, Rowen JL, 2007). Although it is assumed that antenatal use of glucocorticoids and nonsteroidal anti-inflammatory drugs increases the risk of SIP, there is not enough data to show this relationship. Exposure to glucocorticoids during the postnatal period increases the risk of SIP. In a meta-analysis of four studies, it was shown that VLBW babies given dexamethasone for bronchopulmonary dysplasia prophylaxis had an increased risk of SIP compared to the control group (Wadhawan R, Oh W, Vohr BR, et al, 2013). Although it was previously reported that indomethacin use increases the risk of SIP, recent publications do not support this association (Gordon PV, Young ML, Marshall DD, 2001, Stark AR, Carlo WA, Tyson JE, et al).

Necrotizing enterocolitis and SIP result in significant mortality and morbidity. It is important to distinguish between NEC and SIP

because the management of the two conditions is different. Making differential diagnosis in the early period reduces mortality and morbidity. While spontaneous intestinal perforation usually presents in the first week of life, NEC is seen after the first week, usually after the baby starts feeding. In spontaneous intestinal perforation, abdominal distension is accompanied by bluish discoloration on physical examination. Pneumoperitoneum may be seen on abdominal imaging, but there is no pneumotizis intestinalis or gas in the portal vein, which are radiological findings of NEC. In some SIP patients, no intestinal gas may be seen on radiographs (Kim E MD, Brandt M MD).

In many case series with spontaneous intestinal perforation, the age at which perforation occurs varies between zero and 15 days, with the average being seven days. In an analysis conducted by Pediatrix Medical Group, it was observed that SIP presented earlier than NEC (average seven days versus 15 days) (Guthrie SO, Gordon PV, Thomas V, et al, 2003).

Babies with spontaneous intestinal perforation present with acute abdominal distension and hypotension. Abdominal swelling usually occurs without symptoms such as erythema, crepitus, and hardening of the abdominal wall seen in NEC. Bluish-black discoloration of the abdominal wall is typically seen in cases of SIP but not in NEC. This discoloration can spread to the groin and, in male babies, to the testicles. In many cases, SIP has been shown to be associated with sepsis caused by coagulase-negative staphylococci or Candida albicans. Sepsis may be a major cause of morbidity and mortality, but it is not clear whether infection occurs before perforation or is a result of perforation (Gordon PV, Young ML, Marshall DD, 2001).

Differentiating between necrotizing enterocolitis and SIP is also important in starting treatment. The definitive treatment for spontaneous intestinal perforation is surgery. The traditional method is explatatory laparotomy and bowel resection, the alternative method is primary peritoneal drainage (PPD). The advantages of

PPD are that it can be performed at the bedside and does not require general anesthesia and laparotomy (Stark AR, Carlo WA, Tyson JE, et al, 2001).

There is no randomized controlled study comparing these two surgical procedures in treatment. In case reports, it has been reported that PPD is generally used as both stabilizing and definitive treatment and most of the patients did not need another surgical intervention (Gordon P, Rutledge J, Sawin R, et al, 1999, Kelleher J, Salas AA, Bhat R et al, 2014, Schmidt B, Davis P, Moddemann D, et al, 2001). In a review comparing primary peritoneal drainage treatment in NEC and SIP cases, it was found that there was no difference in terms of benefit and mortality between the two groups (Paquette L, Friedlich P, Ramanathan R, Seri I, 2006).

In the primary peritoneal drainage technique, a drain is placed in the abdomen and intestinal content and meconium drainage is monitored. When there is no intestinal content and meconium drainage from the drain area, the drain is monitored daily until it is completely removed. Situations requiring laparotomy after this procedure include reaccumulation of free air after removal of the drain and ongoing sepsis (indicating that the perforated bowel section has not healed), fistula with persistent intestinal drainage that does not close for several weeks, adhesion in the perforation area, and more often due to stricture. It is the intestinal obstruction that occurs (Paquette L, Friedlich P, Ramanathan R, Seri I, 2006).

Conclusion

Prematurity is the most important risk factor for necrotizing enterocolitis, which is the most important acquired gastrointestinal system disease seen in newborn babies. Although survival rates increase with early diagnosis and treatment, it still maintains its importance as it is still an important cause of mortality and morbidity, especially in VLBW babies.The most concerning condition for necrotizing enterocolitis, which is seen especially in babies followed in neonatal intensive care units and primarily affects

the gastrointestinal system, is prematurity. Although promising results are obtained with early diagnosis and treatment, VLBW is an entity that needs to be taken into consideration due to the possibility of mortality and morbidity, especially in newborns. Reducing the rate of prematurity in newborn babies, breastfeeding, preventing chorioamnionitis and infections that may occur in the neonatal period, trophic nutrition, appropriate prenatal care, maternal steroid use are valuable in preventing NEC. Although promising results have been observed regarding the use of probiotics in newborn babies, it can be thought that good results can be obtained with adequate intake results regarding dose, timing, treatment duration and bacterial colonization.

References

Neu J. Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. Pediatr, Clin North Am 1996; 43:409.

Kosloske AM. Epidemiology of necrotizing enterocolitis. Acta Paediatr Suppl 1994; 396:2.

Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants, 1991- 1999. Pediatrics 2002; 110:143.

Sankaran K, Puckett B, Lee DS, et al. Variations in incidence of necrotizing enterocolitis in Canadian neonatal intensive care units. J PediatrGastroenterolNutr 2004; 39:366.

Lee SK, McMillan DD, Ohlsson A, et al. Variations in practice and outcomes in the Canadian NICU network: 1996-1997. Pediatrics 2000; 106:1070.

Schanler RJ. Clinical features and diagnosis of necrotizing enterocolitis in newborns. In: UpToDate, Abrams SA Nov 13 2015

Ostlie DJ, Spilde TL, St Peter SD, et al. Necrotizing enterocolitis in full-term infants. J PediatrSurg 2003; 38:1039.

Lambert DK, Christensen RD, Henry E, et al. Necrotizing enterocolitis in term neonates: data from a multihospital healthcare system. J Perinatol 2007; 27:437.

Short SS, Papillon S, Berel D, et al. Late onset of necrotizing enterocolitis in the full-term infant is associated with increased mortality: results from a two-center analysis. J Pediatr-Surg 2014; 49:950.

Kliegman RM, Walker WA, Yolken RH. Necrotizing enterocolitis: research agenda for a disease of unknown etiology and pathogenesis. Pediatr Res 1993; 34:701.

Holman RC, Stoll BJ, Clarke MJ, Glass RI. The epidemiology of necrotizing enterocolitis infant mortality in the United States. Am J Public Health 1997; 87:2026.

Morriss FH Jr, Moore M, Gibson T, West MS. Motility of the small intestine in preterm infants who later have necrotizing enterocolitis. J Pediatr 1990; 117:S20.

Bauer CR, Morrison JC, Poole WK, et al. A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. Pediatrics 1984; 73:682.

Halac E, Halac J, Bégué EF, et al. Prenatal and postnatal corticosteroid therapy to prevent neonatal necrotizing enterocolitis: a controlled trial. J Pediatr 1990; 117:132.

Clark DA, Miller MJ. Intraluminal pathogenesis of necrotizing enterocolitis. J Pediatr 1990; 117:S64.

Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011;:CD001241.

Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2014;12:CD001970.

La Gamma EF, Browne LE. Feeding practices for infants weighing less than 1500 G at birth and the pathogenesis of necrotizing enterocolitis. ClinPerinatol 1994; F:271.

Schanler RJ, Shulman RJ, Lau C, et al. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. Pediatrics 1999; 103:434.

Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev 2009; :CD000504.

Hunter CJ, Upperman JS, Ford HR, Camerini V. Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). Pediatr Res 2008; 63:117.

Hooper LV, Wong MH, Thelin A, et al. Molecular analysis of commensal host-microbial relationships in the intestine. Science 2001; 291:881.

Patel RM, Denning PW. Intestinal microbiota and its relationship with necrotizing enterocolitis. Pediatr Res 2015; 78:232.

Stewart CJ, Marrs EC, Magorrian S, et al. The preterm gut microbiota: changes associated with necrotizing enterocolitis and infection. ActaPaediatr 2012; 101:1121.

Jacquot A, Neveu D, Aujoulat F, et al. Dynamics and clinical evolution of bacterial gut microflora in extremely prematüre patients. J Pediatr 2011; 158:390.

Alexander VN, Northrup V, Bizzarro MJ. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizingm enterocolitis. J Pediatr 2011; 159:392.

Cotten CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremelylow birth weight infants. Pediatrics 2009; 123:58.

Stuart RL, Tan K, Mahar JE, et al. An outbreak of necrotizing enterocolitis associated with norovirus genotype GII.3. Pediatr Infect Dis J 2010; 29:644.

Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet 2006;368:1271.

Warner BB, Ryan AL, Seeger K, et al. Ontogeny of salivary epidermal growth factor and necrotizing enterocolitis. J Pediatr 2007; 150:358.

Schanler RJ. Pathology and pathogenesis of necrotizing enterocolitis in newborns. In: UpToDate, Abrams SA Jan 18 2016

Mohamed A, Shah PS. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. Pediatrics 2012; 129:529.

Stritzke AI, Smyth J, Synnes A, et al. Transfusion-associated necrotising enterocolitis in neonates. Arch Dis Child Fetal Neonatal Ed 2013; 98:F10.

Keir AK, Wilkinson D. Question 1 * do feeding practices during transfusion influence the risk of developing necrotising enterocolitis in preterm infants? Arch Dis Child 2013;98:386

Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006; 117:e137.

Rao SC, Basani L, Simmer K, et al. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database Syst Rev 2011; :CD006182.

Tepas JJ 3rd, Sharma R, Leaphart CL, et al. Timing of surgical intervention in necrotizing enterocolitis can be determined by trajectory of metabolic derangement. J PediatrSurg 2010; 45:310.

Schanler RJ.Management of necrotizing enterocolitis in newborns. In: UpToDate, Abrams SA Oct 15 2015.

Duro D, Kalish LA, Johnston P, et al. Risk factors for intestinal failure in infants with necrotizing enterocolitis: a Glaser Pediatric Research Network study. J Pediatr 2010; 157:203.32.

Kim E MD, Brandt M MD. Spontaneous intestinal perforation of the newborn In: UpToDate Garcia-Prats J, MD.

Ragouilliaux CJ, Keeney SE, Hawkins HK, Rowen JL. Maternal factors in extremely low birth weight infants who develop spontaneous intestinal perforation. Pediatrics 2007; 120:e1458.

Wadhawan R, Oh W, Vohr BR, et al. Spontaneous intestinal perforation in extremely low birth weight infants: association with

indometacin therapy and effects on neurodevelopmental outcomes at 18-22 months corrected age. Arch Dis Child Fetal Neonatal Ed 2013; 98:F127.

Gordon PV, Young ML, Marshall DD. Focal small bowel perforation: an adverse effect of early postnatal dexamethasone therapy in extremely low birth weight infants. J Perinatol 2001;21:156.

AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 2001; 344:95.

Guthrie SO, Gordon PV, Thomas V, et al. Necrotizing enterocolitis among neonates in the United States. J Perinatol 2003;23:278.

Gordon PV, Young ML, Marshall DD. Focal small bowel perforation: an adverse effect of early postnatal dexamethasone therapy in extremely low birth weight infants. J Perinatol 2001;21:156.

Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 2001; 344:95.

Gordon P, Rutledge J, Sawin R, et al. Early postnatal dexamethasone increases the risk of focal small bowel perforation in extremely low birth weight infants. J Perinatol 1999; 19:573.

Kelleher J, Salas AA, Bhat R, et al. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics 2014; 134:e1369.

Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001; 344:1966.

Paquette L, Friedlich P, Ramanathan R, Seri I. Concurrent use of indomethacin and dexamethasone increases the risk of spontaneous intestinal perforation in very low birth weight neonates. J Perinatol 2006; 26:486.

CHAPTER II

Approach To Fever of Unknown Origin In Children

Sadiye SERT[1]

Introduction

Fever is one of the most prevalent reasons for paediatric emergency room visits (Wing, Dor & McQuilkin, 2013). In most circumstances, the source of the fever may be recognized and treated swiftly (Antoon &, et al., 2015). The family and the doctor are concerned since the fever has persisted and no cause has been identified (Élise, 2017). Despite the advancements in science and technology, fever of unknown origin (FUO) continues to be a significant and challenging issue for paediatricians (Tezer & et al, 2012).

Definition

Petersdorf and Beeson developed the phrase "FUO" in 1961 (Petersdorf & Beeson, 1961). There is currently no universally

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accepted definition of fever of unknown cause. Recent studies, however, define FUO as a temperature of 38.0°C (100.4°F) or higher that lasts at least 8 days and has no evident explanation (Haidar & Singh, 2022, Antoon &, et al., 2015). While some publications define FUO as lasting three weeks in outpatients, it is determined one week later in hospitalized children (Cabanalan & Gonzales, 2017). These temporal definitions are no longer relevant in the age of molecular diagnostic testing (Chusid, 2017). The underlying cause of fever of unknown origin might be a curable or life-threatening condition. As a result, physicians face a difficult scenario in the patient's initial application (Steenhoff, 2020). Although the terms "FUO" and "fever without source" are used interchangeably in clinical practice, they are not the same thing. Fever without source is defined as a fever lasting one week or less that does not have a sufficient explanation despite a complete medical history and physical examination (Ondrušová, 2015). If no fever focus is discovered after 7 days, fever without source might proceed to FUO. In some individuals, despite a history, physical examination, and laboratory tests, a diagnosis cannot be determined, and the duration of fever is extended.

Aetiology

It's unclear just how often FUO in children (Antoon, Potisek& Lohr, 2015). In children with FUO, infectious illnesses, connective tissue disorders, and neoplasms are the most prevalent etiological causes, while uncommon diseases and common diseases may play a role. The potential occurrence of drug-induced fever should be taken into account in the event that the patient is receiving any form of medication. Drug fever typically endures and is not accompanied by any other symptoms. The discontinuation of the medication is correlated with the resolution of the fever, typically occurring within a span of 72 hours. If there is suspicion of factitious fever, which involves introducing pyogenic material or tampering with the thermometer by either the patient or parent, it is essential to record the occurrence and characteristics of the fever within the hospital

setting. It is crucial to conduct prolonged and uninterrupted monitoring of the patient, which may involve the utilization of electronic or video surveillance (Steenhoff, 2020).

The most frequent causative factors for FUO in children are shown in Table 1 (Dayal& Agarwal, 2016). The distribution of aetiologies in FUO is influenced not only by the availability of new diagnostic techniques and radiography approaches, but also by geographical factors. Age of the child and the season of the research were revealed to have an impact on the distribution of causative agents in FUO. A research study was conducted in Egypt, wherein a sample of 127 children who were diagnosed with FUO underwent examination. The investigation yielded findings indicating that infectious diseases were detected in 36.2% of the children, while various underlying factors were identified in 29.9% of the cases. Additionally, collagen vascular diseases were observed in 10.2% of the children, and neoplastic diseases were found in 7.8% of the cases. Nonetheless, a conclusive diagnosis could not be reached for 15.7% of the children (Hassan, Ashraf &Shaimaa, 2014). In another study carried out in Peru, a cohort of 100 children who presented with FUO was subjected to examination. It was observed that approximately half of the children were below the age of two years. Among this group of children, infectious disease was detected in 48% of cases, neoplastic disease in 6%, and other causes in 2%. However, a definitive diagnosis could not be established in 44% of the cases (Cerdán&, et al., 2021). In a separate study conducted in China spanning a duration of 7 years, a cohort of 1288 children suffering from FUO was included. The analysis of this group revealed that infectious diseases were detected in a substantial proportion of the children, specifically 50.9%. Furthermore, non-infectious inflammatory diseases were identified in 4.9% of the cases, neoplastic diseases in 6.7%, and other causes in 26.6% of the cases. It is worth noting that a conclusive diagnosis could not be reached in 10.9% of the cases (Hu&, et al., 2022). A retrospective study conducted in a central location in Turkey in 2012 established the aetiology of 69 of 77 children with FUO. In this study infectious

diseases (50.7%), malignancy (14.4%), collagen vascular disorders (7.2%), and other diseases (27.5%) were the most prevalent diagnosis, respectively (Tezer & et al, 2012). Similarly, a study conducted in Taiwan in 2017 included a cohort of 93 children with FUO. The findings of this study revealed that infectious disease was responsible for 37.6% of the cases, while neoplastic disease was detected in 17.2% of the cases. Furthermore, various causes were observed in 16.2% of the cases, whereas collagen vascular disease accounted for 14% of the cases. Notably, in 15.1% of the cases, no specific etiological cause could be identified (Chien&, et al. 2017). Although reaching a definitive diagnosis is unattainable, frequently the fever dissipates (Palazzi, 2023a). In a comprehensive evaluation of 18 studies including 1638 children, infections were shown to be responsible for 51% of FUO, with bacterial infections accounting for 59% of infections. Among bacterial illnesses, *Bartonella* infections are more common in industrialized nations, whereas brucellosis and tuberculosis are more common in underdeveloped countries. In wealthy nations, viral infections, particularly Epstein–Barr virus, are rather common (Chow& Robinson, 2011).

Connective tissue disorders (systemic juvenile idiopathic arthritis) are the second most common cause of FUO in children, behind infectious infections (Chow& Robinson, 2011, Antoon &, et al., 2015).

The third most frequent cause of FUO is neoplastic disorders. Lymphoma and leukemia are the most prevalent neoplasias that cause FUO (Attard & et al.,2018). It represented 7% in the Pizzo et al. patient series (Chouchane& et al., 2004.], 15% and 13% in the Lohr and Hendley series, respectively (Lohr JA&Hendley JO, 1977).

Despite extensive examinations, the definitive diagnosis in about one-third of children with FUO cannot be identified (Antoon &, et al., 2015, Gaeta, Fusco & Nardiello, 2006). Approximately 25% of children experiencing FUO exhibit febrile episodes that resolve spontaneously without reaching a definitive diagnosis

(Chow& Robinson, 2011). This is most likely related to undetected viral infections (Colvin & et al., 2012).

Table 1: The aetiology of FUO in children

1.Infectious diseases
Bacterial
Systemic
Tuberculosis
Salmonellosis
Brucellosis
Leptospirosis
Localized
Liver abscess
Mastoiditis
Infective endocarditis
Osteomyelitis
Pelvic abscess
Pyelonephritis
Sinusitis
Subdiaphragmatic abscess
Viral
Cytomegalovirus
Hepatitis viruses
Epstein –Barr viruses
Rickettsial
Q fever
Fungal
Blastomycosis
Histoplasmosis
Parasitic
Toxoplasmosis
Malaria
2.Connective tissue disorders
Systemic Lupus Erythematosus
Juvenile Idiopathic Arthritis
Polyarteritis Nodosa
Kawasaki disease
3. Neoplastic disorders
Hodgkin disease
Leukemia
Lymphoma
Neuroblastoma
4.Other causes
Drug fever
Ectodermal dysplasia
Factitious fever
Periodic fever syndromes
Serum sickness
Drug fever

Diagnostic evaluation

In FUO, a thorough medical history and physical examination remain the cornerstones of the diagnostic process. Therefore, opting for differential diagnosis would be a more convenient option. It is highly recommended to follow a systematic approach, avoiding any invasive or costly examinations (Antoon &, et al., 2015).

Anamnesis

In order to determine the underlying cause of the child's FUO, a thorough history should be taken first. If the child is suspected of having FUO, a full history might help to speed up the diagnosis. The presence of a fever in the patient who is reported to have one should first be objectively confirmed. In the medical history, it is essential to inquire about the fever pattern, the accompanying symptoms of the fever, the persistence of constitutional symptoms after the fever resolves, the presence of sweating during the fever, the correlation between the fever and sweating, the existence of ocular redness, nasal discharge, recurrent pharyngitis with ulceration, gastrointestinal symptoms, and joint or bone pain (Palazzi, 2023b).

Pseudo-FUO is characterized as consecutive episodes of benign, self-limited infections accompanied by fever that is perceived by the parents as one extended bout of fever. It is imperative to thoroughly eliminate this possibility before embarking on an unnecessary evaluation. Typically, pseudo-FUO commences with a distinct infection (often of viral origin) that resolves, only to be succeeded by additional febrile viral illnesses that may be less clearly defined (Steenhoff, 2020). A child manifesting symptom of a prolonged febrile illness may potentially be undergoing a "pseudo-FUO," which is a sequence of successive self-restricted minor infections. This scenario is particularly plausible when said child is an only child residing in a household and commencing their school attendance for the first time, or if they have older siblings who introduce infectious agents into the home. The fever diary may offer hints as to a potential underlying condition if fever is verified

(Chusid, 2017). The duration and configuration of the elevated body temperature ought to be explicitly examined during the medical evaluation. Given that diseases may present themselves at various stages of life, it is judicious to conceptualize them in relation to specific age cohorts. Adolescent patients, for instance, are more likely to develop tuberculosis. For tuberculosis in particular, a thorough history should be taken regarding contact with sick individuals. It is necessary to obtain a history of contact with wild or domestic animals (Dayal& Agarwal, 2016). If brucellosis is suspected, consumption of unpasteurized milk or unripe cheese should be questioned (Wu& et al., 2022). Furthermore, in places where Crimean-Congo hemorrhagic fever is endemic, tick bite history should be explored (Oygar& et al., 2023). It is of utmost importance to possess knowledge regarding one's medical background in the event that a child has previously ingested food or beverages that were tainted. It is of significant significance to ascertain details relating to the utilization of medications that may impact the control system responsible for regulating body temperature (Dayal& Agarwal, 2016).

Physical Examination

In the situation of paediatric patients who present with an FUO, it is crucial to consider labile blood pressure, tachypnea, relative bradycardia, weight loss, and short stature as part of the overall evaluation. Subsequently, it becomes essential to perform a comprehensive and detailed assessment of each individual, which involves a thorough examination from the cranial to the pedal region (Palazzi, 2023b). By employing a discerning approach that relies on positive signs, the need for superfluous additional evaluations can be averted. A comprehensive physical examination is imperative to investigate any indications pertaining to the underlying diagnosis, and frequently, it is advantageous to conduct a thorough examination on separate occasions to identify any alterations or omissions in signs (Steenhoff, 2020.). In a child with FUO, it is critical to assess the overall look in terms of red flag findings and systemic

involvement (Marshall, 2014). The most prominent "red flags" include a terrible look, anorexia or asthenia, pale skin and mucous membranes, petechiae, diffuse lymphadenopathy or hepatosplenomegaly, dehydration, and severe bone pain. It may be important to notice in certain circumstances in terms of fever decrease or the emergence of accompanying signs as a consequence of anamnesis and medical examination (Attard & et al., 2018).

Laboratory investigation

Examinations can be conducted either as an inpatient or as an outpatient, contingent upon the clinical state of the individual (Steenhoff, 2020). Recently, some clinicians have recommended a complete blood count, peripheral smear, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal and liver functions, muscle enzymes, lactate dehydrogenase (LDH), urinalysis, and urine culture in the first-line laboratory evaluation of children with FUO. The clinical suspicion should direct any additional first-level work-up, which may entail a chest x-ray, echocardiography, and abdomen ultrasound. Patients who have significant symptoms and signs during the history-taking and physical examination should undergo further testing. In the context of second-level examinations, it is imperative to conduct comprehensive evaluations for suspected ailments. These evaluations encompass the administration of targeted tests and imaging techniques to identify infectious diseases, neoplastic conditions, connective tissue disorders, immunodeficiencies, as well as gastrointestinal ailments. (Attard & et al., 2018, Palazzi, 2023b).

Anomalous complete blood count or blood smear analysis may offer indications to the fundamental diagnosis (Palazzi, 2023b). Direct examination of a blood smear stained with Giemsa can serve as a diagnostic tool for patients suspected to have malaria in areas that are endemic to the disease (Shahbodaghi & Rathjen, 2022). Serological inflammatory indicators are among the most helpful data in the assessment of children with fever. These markers had a significant rise in infants, which suggests a potentially dangerous

inflammatory process. Even while procalcitonin and CRP levels can be vulnerable to false negatives early in the course of illness, more recent assays like procalcitonin levels are very helpful in determining the existence of an inflammatory syndrome in its initial stages. ESR, on the other hand, have a problem with being quite delayed in reaching their elevated levels, sometimes up to a week after the onset of the disease, and then may be quite slow to return to normal during recovery. This compromises its diagnostic utility during the early stages of an inflammatory illness and limits its usefulness in gauging therapeutic response. The serialization of these tests may be helpful in assessing the level of inflammation and the effectiveness of the therapy (Chusid, 2017). Routine blood cultures have the potential to yield a definitive diagnosis in pediatric patients afflicted with bacteremia, infective endocarditis, typhoid fever, or brucellosis (Palazzi, 2023b).

Radiological imaging methods

An assessment of the abdominal region should be recommended for paediatric patients displaying persistent fever, elevated ESR and CRP levels, reduced appetite, and weight loss in order to rule out the possibility of inflammatory bowel disease, particularly if the child exhibits gastrointestinal issues, with or without anaemia. Abdominal abscesses, tumors, and lymphadenopathy can be detected through the use of ultrasound (USG), computed tomography (CT), and magnetic resonance imaging (MRI) (Ondrušová, 2015). Recent studies showed that 18F-FDG PET/CT to be a valuable tool for investigation and management in children with FUO (van Rijsewijk & et al, 2023. Pijl & et al., 2020, Jasper & et al., 2010).

Treatment of FUO in children

The management of FUO in paediatric patients necessitates the establishment of a confirmed diagnosis of the underlying pathology. Administration of antipyretic agents should be withheld until such time that the diagnosis is ascertained. Moreover, antibiotics should

only be administered in cases where the causative infectious organism has been definitively identified. However, in instances where the underlying disease is identified and fever is accompanied by negative symptoms, antipyretic agents may be administered (Steenhoff, 2020).

Conclusion

References

1. Antoon, J.W., Potisek, N.M., & Lohr, J.A (2015) Pediatric Fever of Unknown Origin. *Pediatrics in review /American Academy of Pediatrics,* 36(9):380-390; quiz 391. Doi: 10.1542/pir.36-9-380
2. Attard, L., Tadolini, M., De Rose, D.U., & Cattalini, M (2018) Overview of fever of unknown origin in adult and paediatric patients. *Clinical and experimental rheumatology*, 110(1):10-24.
3. Cabanalan-Rivera, F.A. & Gonzales L.M.A.M (2017) Fever Of Unknown Origin In Children: A Five-Year. *Pediatric Infectious Diseases Society of the Philippines Journal*, 18(1):36 -44.
4. Cerdán-Rojas, S., Candela-Herrera, J., Flores-Lovon, K., & Gutiérrez-Ingunza E.L(2021) Fiebre de origen desconocido en niños: experiencia de 5 años en un hospital pediátrico de Perú. *Revista mexicana de pediatría* 88.5:179-183.
5. Chien, Y.L., Huang, F.L., Huang, C.M., &Chen, P.Y (2017) Clinical approach to fever of unknown origin in children. *Journal of Microbiology, Immunology and Infection* 50(6):893-898. Doi: 10.1016/j.jmii.2015.08.007
6. Chouchane, S., Chouchane, C.H., Ben, Meriem C.H., Seket, B., Hammami, S., Nouri, S., Monastiri, K., &Guediche, M.N (2004) Les fièvres prolongées de l'enfant. Etude rétrospective de 67 cas [Prolonged fever in children. Retrospective study of 67 cases]. *Archives de pédiatrie*. 11:1319-1325. French. Doi: 10.1016/j.arcped.2004.07.018
7. Chow, A., &Robinson, J.L (2011) Fever of unknown origin in children: a systematic review. *World journal of paediatrics* 7(1):5-10. Doi: 10.1007/s12519-011-0240-5.
8. Chusid, M.J (2017) Fever of Unknown Origin in Childhood. *Pediatric Clinics of North America* 64(1):205-230. Doi: 10.1016/j.pcl.2016.08.014

9. Colvin, J.M., Muenzer ,J.T., Jaffe, D.M., Smason, A., Deych, E., Shannon, W.D., Arens, M.Q., Buller, R.S., Lee, W.M., Weinstock, E.J., Weinstock, G.M., & Storch, G.A (2012) Detection of viruses in young children with fever without an apparent source. *Pediatrics*.130(6):e1455-1462. Doi: 10.1542/peds.2012-1391

10. Dayal, R., & Agarwal, D (2016) Fever in Children and Fever of Unknown Origin. *Indian journal of paediatrics*. 83(1):38-43. Doi: 10.1007/s12098-015-1724-4

11. Élise W (2017). Fever of Unknown Origin. In: McInerny, T.K., Adam, H.M., Campbell, D.E., DeWitt, T.G., Foy, J.M., Kamat, D.M., (Eds). *American Academy of Pediatrics Textbook of Pediatric Care*. (2nd ed., pp.1361-1365). Elk Grove Village, IL: American Academy of Pediatrics.

12. Gaeta, G.B., Fusco, F.M., &Nardiello, S. (2006). Fever of unknown origin: a systematic review of the literature for 1995-2004. *Nuclear medicine communications*. 27(3):205-211. Doi: 10.1097/00006231-200603000-00002

13. Haidar, G. &Singh, N (2022) Fever of Unknown Origin. *The New England journal of medicine*. 386:463-477. Doi: 10.1056/NEJMra2111003

14. Hassan, R.H., Fouda, A.E., & Kandil, S.M. (2014) Fever of Unknown Origin in Children: A 6 year- Experience in a Tertiary Pediatric Egyptian Hospital. *International journal of health sciences*. 8(1):13-9. Doi: 10.12816/0006067.

15. Hu, B., Chen, T.M., Liu, S.P., Hu, H.L., Guo, L.Y., Chen, H.Y., Li, S.Y., & Liu, G (2022) Fever of unknown origin (FUO) in children: a single-centre experience from Beijing, China. *BMJ Open*. 12(3):e049840. Doi: 10.1136/bmjopen-2021-049840

16. Jasper, N., Däbritz, J., Frosch, M., Loeffler, M., Weckesser, M., & Foell, D (2010) Diagnostic value of [(18)F]-FDG PET/CT in children with fever of unknown origin or unexplained signs of

inflammation. *European journal of nuclear medicine and molecular imaging*. 37(1):136-145. Doi: 10.1007/s00259-009-1185-y

17. Lohr, J.A. & Hendley, J.O (1977) Prolonged fever of unknown origin: a record of experiences with 54 childhood patients. *Clinical pediatric*. 16(9):768-73. Doi: 10.1177/000992287701600905
18. Marshall, G.S (2014) Prolonged and recurrent fevers in children. *The Journal of infection*.68 (Suppl 1):S83-93. Doi: 10.1016/j.jinf.2013.09.017
19. Ondrušová, A (2015). Approach To Fever Of Unknown Origin In Children. *University Review.* 9 (2-3):72-77
20. Oygar, P.D., Gürlevik, S.L., Sağ, E., İlbay, S., Aksu, T., Demir, O.O., Coşgun, Y., Eyüpoğlu, S.A., Karakaya, J., Cangül, Ş.Ü., Cengiz, A.B., & Özsürekci, Y. (2023) Changing Disease Course of Crimean-Congo Hemorrhagic Fever in Children, Turkey. *Emerging infectious diseases.* 29(2):268-277. Doi: 10.3201/eid2902.220976
21. Palazzi DL (2023) Fever of unknown origin in children: Etiology. (https://www.uptodate.com/contents/fever-of-unknown-origin-in-children-etiology?search=Fever%20of%20unknown%20origin%20in%20children:%20Etiology&source=search_result&selectedTitle=1~73&usage_type=default&display_rank=1 (Accessed 20th September 2023.)
22. Palazzi DL (2023) Fever of unknown origin in children: Evaluation. (https://www.uptodate.com/contents/fever-of-unknown-origin-in-children-evaluation?search=Fever%20of%20unknown%20origin%20in%20children:%20Evaluation&source=search_result&selectedTitle=1~73&usage_type=default&display_rank=1 (Accessed 20th September 2023.)

23. Petersdorf, R.G. & Beeson, P.B (1961) Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore).*40:1-30. Doi: 10.1097/00005792-196102000-00001

24. Pijl, J.P., Kwee, T.C., Legger, G.E., Peters, H.J.H., Armbrust, W., Schölvinck, E.H., & Glaudemans, A.W.J.M (2020) Role of FDG-PET/CT in children with fever of unknown origin. *European journal of nuclear medicine and molecular imaging.* 47(6):1596-1604. Doi: 10.1007/s00259-020-04707-z

25. Shahbodaghi, S.D. & Rathjen, N.A (2022) Malaria: Prevention, Diagnosis, and Treatment. *American family physician.* 106(3):270-278.

26. Steenhoff, A.P Fever of Unknown Origin. (2020) In: Kliegman, R.M., Joseph, W.S.G., &Blum, N.J. (Eds). *Nelson Textbook of Pediatrics*, (21nd ed., pp. 1397-1402.e1). Philadelphia, PA: Elsevier.

27. Tezer, H., Ceyhan, M., Kara, A., Cengiz, A.B., Devrim, İ., &Seçmeer, G. (2012) Fever of unknown origin in children: the experience of one center in Turkey. *The Turkish journal of pediatrics*. 54(6):583-589.

28. van Rijsewijk, N.D., IJpma, F.F.A., Wouthuyzen-Bakker, M., & Glaudemans, A.W.J.M. (2023) Molecular Imaging of Fever of Unknown Origin: An Update. *Seminars in nuclear medicine*. 53(1):4-17. Doi: 10.1053/j.semnuclmed.2022.07.002.

29. Wing, R., Dor, M.R., & McQuilkin, P.A (2013) Fever in the pediatric patient. *Emergency medicine clinics of North America.* .31(4):1073-1096. Doi: 10.1016/j.emc.2013.07.006

30. Wu, Z.G., Song, Z.Y., Wang, W.X., Xi, W.N., Jin, D., Ai, M.X., Wu, Y.C., Lan, Y., Song, S.F., Zhang, G.C., Yao, X.B., Gao, Z., Liu, C.Y., Sun, K., Yu, D.S., Xie, B.G., &Sun, S.L. (2022) Human brucellosis and fever of unknown origin. *BMC infectious diseases*. 22(1):868. Doi: 10.1186/s12879-022-07872-8

CHAPTER III

Croup: Diagnostics and Management

Gülfer AKÇA[1]

Introduction

The larynx is a complex organ consisting of membranes, ligaments and muscles on a cartilage structure in the midline of the neck, located between the root of the tongue and the trachea. Infectious diseases of the larynx, which provide phonation and protect the upper and lower respiratory tract, can be an important and urgent situation because they are related to the respiratory tract.

Approach to Laryngeal Diseases

As with all diseases, it is necessary to take a very good anamnesis for conditions related to the larynx. The main symptoms in diseases of the larynx are hoarseness, shortness of breath, pain, cough and hemoptysis. The duration of onset of these complaints is

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very important. The presence of hoarseness for a long time requires the exclusion of malignancy. In the follow-up of upper respiratory tract infection, infectious inflammatory diseases should be considered in hoarseness with additional complaints such as cough and fever. Questioning the diseases, medications used and even eating habits is extremely important in terms of diagnosis.

It is essential to perform a careful head and neck examination for patients with complaints about the larynx. The larynx is an area that cannot be seen by direct examination. With inspection, the movements of the larynx, its position should be examined, and the sounds that occur during breathing should be taken into account. Collapse of the stridor and suprasternal notch that occurs during inspiration may be caused by obstruction of the larynx. The location of the larynx should be palpated during both respiration and swallowing, and attention should be paid to the presence of pain and deformity. When more detailed evaluation of the laryngeal structures is required, rigid endoscopes that look down from the mouth or bendable endoscopes that are passed through the nasal cavity and lowered to the level of the hypopharynx can be used. It is also possible to examine the larynx and hypopharynx directly with a rigid laryngoscope. With this procedure, which can be performed under anesthesia, diagnosis and treatment can be performed with detailed examination and, when necessary, biopsy and microlaryngeal surgery. Direct radiographs, computed tomography and magnetic resonance imaging may be requested to assist in the diagnosis of laryngeal diseases (Akyıldız, Çiler Büyükatalay & Dursun 2019). In case of suspicion of foreign bodies and infectious conditions, obstructive formations in the respiratory tract can be identified by direct X-ray. In laryngeal infections, as in all infectious conditions, systemic local symptoms such as fever, leukocytosis, and increased CRP can be observed.

Etiology and Epidemiology of Croup

Croup often see in childhood, is one of the important conditions related to the larynx. It is more common in boys than in

girls (1.5:1). Although the incidence of croup is highest between six months and three years of age, it can also occur in children up to six years of age or, in atypical cases, in children younger than six months (Lee et al. 2015).

It is the most common cause of acute upper airway obstruction in young children. The annual incidence of croup ranges from 1.5 to 6 cases per 100 children younger than 6 years of age (Fitzgerald 2006, Denny et al. 1983). A retrospective Belgian study found that 16% of children aged 5-8 years had croup at least once. (Van Bever et al. 1999)

Croup often presents with a low-grade fever ant cold that lasts for 12 to 72 hours, similar to an upper respiratory tract infection. Croup is characterized by the sudden onset of a barking cough, inspiratory stridor, hoarseness ant respiratory distress due to upper respiratory tract obstruction, mostly at night. These complaints should be differentiated from acute epiglottitis, bacterial tracheitis or inhaled foreign body related to the upper airway.

Croup is a viral disease ant the most common causative agent is Parainfluenza virüs 1,2,3 ant Influenza A. Respiratory syncytial virüs, rhinovirus, adenovirus an deven enterovirus can also cause croup. Bacterial croup is less common ant can be cased by Mycoplasma pneumoniae ant Corynebacterium diphtheriae. Whether the infectious agent is viral or bacterial does not affect the results or initial management (Cherry 2008). It found that 5% of children experienced recurrent croup (>3 attacks), although it is more common in the winter season (Van Bever et al 1999), but sometimes recurrent episodes of croup are a symptom rather than a separe disease. Recurrent croup requires investigation of an underlying cause. Conditions such as airway anormalies, asthma ant gastroesophageal reflux must be distinguished (Quraishi & Lee 2022).

About 85% of cases are describes as mild an less than 1% meet criteria for severe croup, which can be distinguished by signs of hypoxia. Less than 5 % of children with croup are hospitalized, ant

only 1% to 3% of them require intubation (Rankin et al. 2013). Especially in children, the subglottic region is the narrowest part of the respiratory tract ant croup is due to edema of this region. Stridor does not appear until about 80% of the airway here is closed. An increase in edema or narrowing muscus plugs can be fatal for this area. Evaluation of the narrowing of the subglottic region (bell tower-pen tip symptom) in the neck-AC X-ray seen in half of the patients is also useful in terms of diagnosis. However, this finding is neither specific nor sensitive to croup ant may be present in patients with epiglottitis, bacterial tracheitis, neoplasm, or thermal injury (Huang 2012).

In the treatment of croup, it is aimed to reduce subglottic mucosal inflammation ant to facilitate the excretion of secretions by making them more liquid.

Croup typically resolves on its own within 48 hours to a week, but a sudden onset ant a harsh cough can be worrisome. (Petrocheilou et al. 2014, Bjornson & Johnson 2013)

Diagnostic Tests

Laboratory studies are rarely needed to diagnose croup. Viral cultures ant rapid antigen testing should be reserved for patients in whom initial therapy is ineffective. (Bjornson ant Johnson 2013) Complete blood count can help distinguish croup from bacterial etiologies of stridor (e.g., bacterial tracheitis, epiglottitis, peritonsillar abscess, retropharyngeal abscess), but it is not specific. Lymphocytosis may suggest a viral etiology (Petrocheilou et al. 2014, Bjornson ant Johnson 2013). Carboxyhemoglobin level may be helpful in determining cases of thermal injury/smoke inhalation, but history alone is usually sufficient for this diagnosis.

Managing the Disease

Depending on the severity of croup, treatment situations vary. Although a scoring system is not required, the most studied ant

widely used is the Westley Croup Score, which is given in table 1. (Westley, Cotton & Brooks 1978)

Figure 1 shows the outpatient management algorithm for children with croup.Bjornson & Johnson 2013, Zoorob, Sidani & Murray 2011) Minimizing agitation in a symptomatic child may help improve symptoms. Placing the child in a comfortable position can help improve the assessment ant treatment process.

Children with hypoxemia or severe respiratory distress should be given oxygen. Despite the fact that humidified air inhalation has historically been used in the treatment of croup, a meta-analysis of three studies (N = 125) found no statistically significant effect on croup scores or hospital admission in patients with moderate croup (Moore & Little 2007).

Heliox is a mixture of helium ant oxygen used for breathing conditions that theoretically increases airflow resistance by reducing the gas density (helium is a low-density gas). Data on the benefit of heliox in the treatment of croup are limited ant not recommended according to a Cochrane review of three conflicting studies (Moraa et al. 2021).

Corticosteroids

Corticosteroids should be used in cases of severe croup. Treatment with dexamethasone provides faster resolution of symptoms (Bjornson et al. 2004). Corticosteroids are thought to act by reducing laryngeal mucosal edema through their anti-inflammatory effects. Improvement in symptom scores was shown in the Cochrane review six ant 12 hours after treatment with a corticosteroid (dexamethasone, budesonide [Rhinocort], or methylprednisolone). Patients treated with corticosteroids also had shorter lengths of stay in the emergency department or hospital, ant the rate of repeat visits was lower. There is no statistically significant difference between corticosteroids ant epinephrine, but patients treated with corticosteroids need less epinephrine. (Russell et al. 2011)

Epinephrine

Epinephrine is thought to improve symptoms through arteriole vasoconstriction in the upper respiratory tract mucosa, resulting in a reduction of croup edema. Epinephrine is typically used in conjunction with corticosteroids because the onset of action is rapid but has a short half-life, while the effect of corticosteroids begins more slowly but has a longer half-life. Epinephrine reduces symptom scores in children with moderate or severe croup ant should be given via the nebuliser at a dose of 0.05 mL of 2.25% racemic epinephrine per kg (maximum dose = 0.5 mL) or 0.5 mL of L-epinephrine 1:1000 per kg. (maximum dose = 5 mL) (Bjornson et al. 2013, Eghbali et al. 2015). The effects of epinephrine subside after one to two hours, so patients should be monitored for at least two hours after administration before discharge (Bjornson et al. 2013).

Although adverse effects of nebulized epinephrine are rare, patients receiving frequent treatment should also keep in mind adverse cardiac effects.

Table 1 Westley Croup Skoru

Clinical sign	**Score**
Level of consciousness	
Normal (including sleep)	0
Disoriented	5
Cyanosis	
None	0
With agitation	4
At rest	5

Clinical sign	**Score**
Stridor	
None	0
When agitated	1
At rest	2
Air entry	
Normal	0
Decreased	1
Markedly decreased	2
Retractions	
None	0
Mild	1
Moderate	2
Severe	3

Total score	**Croup severity**
≤ 2	Mild
3 to 7	Moderate
8 to 11	Severe
≥ 12	Impending respiratory failure

Adapted with permission from Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. Am J Dis Child. *1978;132(5):48*

CLINICAL ASSESSMENT OF CROUP SEVERITY

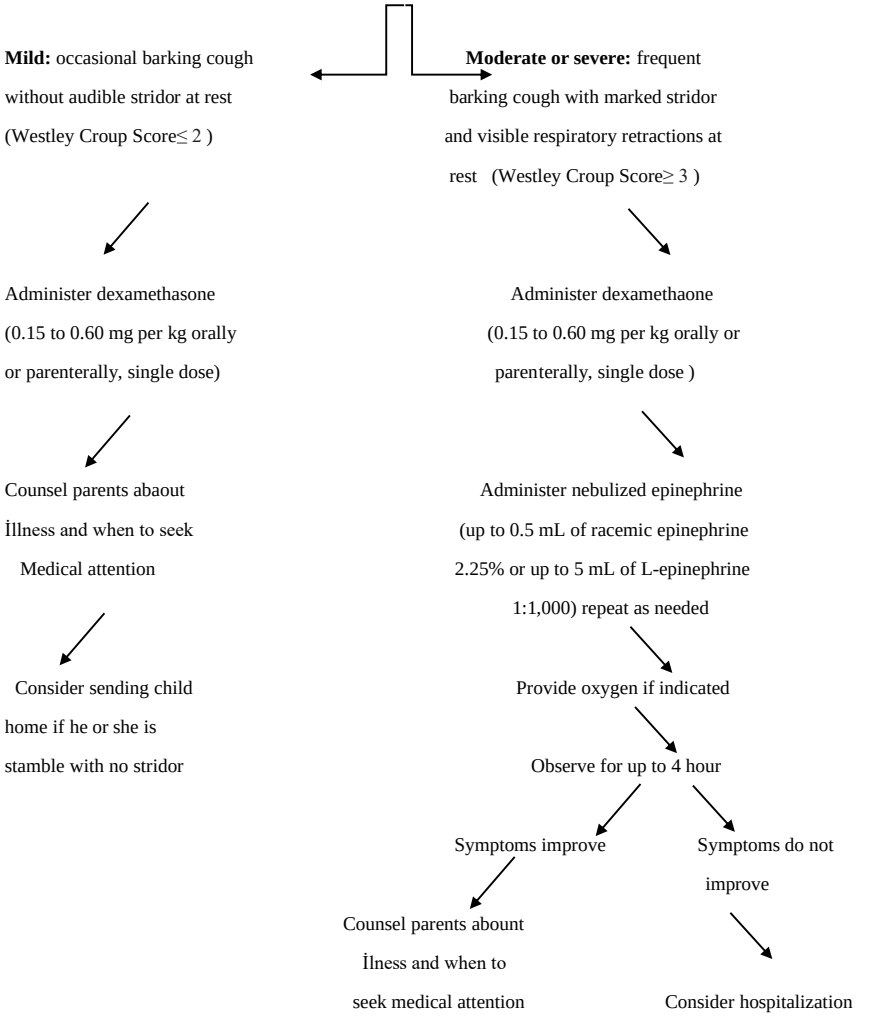

Figure 1. Algorithm for the management of croup

Adapted with permission from Zoorob R, Sidani M, Murray J. Croup: an overview. Am Fam Physician. 2011;83(9):1071, with additional information from references 6, and 21 through 26.

Conclusion

References

Fitzgerald DA.(2006). The assessment and management of croup.*Paediatr.Respir Rev* 7:73–81.2 https://doi.org/10.1016/j.prrv.2005.09.002

Denny FW, Murphy TF, Clyde WA Jr, Collier AM, Henderson FW. (1983). Croup:An 11-year study in a pediatric practice.*Pediatrics*1983;71:871–6 Doi:10.1542/peds.71.6.871

Van Bever HP, Wieringa MH, Weyler JJ, Nelen VJ, Fortuin M, Vermeire PA (1999). Croup and recurrent croup: their association with asthma and allergy. An epidemiological study on 5-8-year-old children. *Eur J Pediatr*. Mar;158(3):253-7. doi: 10.1007/s004310051062.

Akyıldız HS, Çiler-Büyükatalay Z, Dursun G (2019). Clinical Characteristics, Diagnosis, Treatment Approaches of Patients with Acute Dyspnea in ENT *Clinic Journal of Ankara University Faculty of Medicin*e;72(1):91-96 DOI: 10.4274/atfm.galenos.2019.09797

Quraishi H, Lee DJ (2022). Recurrent Croup. *Pediatr Clin North Am*. Apr;69(2):319-328. doi: 10.1016/j.pcl.2021.12.004. PMID: 35337542.

Petrocheilou A, Tanou K, Kalampouka E, Malakasioti G, Giannios C, Kaditis AG.(2014). Viral croup: diagnosis and a treatment algorithm. *Pediatr Pulmonol*. 49(5):421-429 Doi:10.1002/ppul.22993

Bjornson CL, Johnson DW. (2013). Croup in children. *CMAJ*. 2013;185(15):1317-1323 Doi: 10.1503/cmaj.121645

Westley CR, Cotton EK, Brooks JG. (1978). Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-

blind study. *Am J Dis Child,* 132(5):484-487 Doi:0.1001/archpedi.1978.02120300044008

Zoorob R, Sidani M, Murray J 2011). Croup: an overview. *Am Fam Physician.* 83(9):1067-1073 PMID: 21534520

Cherry JD.(2008). Clinical practice. Croup. *N Engl J Med.* 358(4):384-391.Doi: 10.1056/NEJMcp072022

Lee DR, Lee CH, Won YK, Youn Kyung Won, Dong In Suh, Eui-Jung Roh, Mi-Hee Lee, Eun Hee Chung, (2015). Clinical characteristics of children and adolescents with croup and epiglottitis who visited 146 emergency departments in Korea. *Korean J Pediatr.* 58(10):380-385. Doi:10.3345/kjp.2015.58.10.380

Huang CT (2012). Steeple sign: not specific for croup. *J Emerg Med.* 43(5):e333-e334. Doi:10.1016/ j.jemermed2011.05.038

Rankin I, Wang SM, Waters A, Clement WA, Kubba H.(2013). The management of recurrent croup in children. *J Laryngol Otol.* 2013 May;127(5):494-500. Doi: 10.1017/S0022215113000418.

Moore M, Little P (2007). Humidified air inhalation for treating croup: a systematic review and meta-analysis. *Fam Pract.* 24(4):295-301 Doi: 10.1093/fampra/cmm022

Moraa I, Sturman N, McGuire T, van Driel ML (2013). Heliox for croup in children. *Cochrane Database Syst Rev.* 2013(12):CD006822. Doi: 10.1002/14651858.CD006822.pub6

Bjornson CL, Klassen TP, Williamson J, Williamson J, Brant R, Mitton C, Plint A, Bulloch B, Evered L Johnson DW (2004). A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med.* 351(13):1306-1313. Doi: 10.1056/NEJMoa033534

Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP (2011). Glucocorticoids for croup. *Cochrane Database Syst Rev.* (1):CD001955. Doi:10.1002/14651858.CD001955.pub3

Bjornson C, Russell K, Vandermeer B, Klassen TP, Johnson DW (2013). Nebulized epinephrine for croup in children. *Cochrane Database Syst Rev.* (10):CD006619. Doi:10.1002/14651858.CD006619.pub2

Eghbali A, Sabbagh A, Bagheri B, Taherahmadi H, Kahbazi M (2016). Efficacy of nebulized L-epinephrine for treatment of croup: a randomized, double-blind study. *Fundam Clin Pharmacol.* 2016;30(1):70-75. Doi: 10.1111/fcp.12158

CHAPTER IV

Use Of Antipsychotics in The Treatment of Major Depression

Çağlar JAİCKS

Introduction

Major depression, also known as clinical depression, is a severe mental health disorder. This condition is characterized by prominent symptoms that negatively impact an individual's daily life, including intense sadness, hopelessness, loss of energy, loss of interest, sleep disturbances, changes in appetite, difficulty concentrating, feelings of worthlessness, and thoughts of suicide. Major depression is a condition in which these symptoms persist continuously for at least two weeks. These symptoms can have a significant impact on an individual's work, school, relationships, and overall quality of life. Depression can also lead to physical symptoms such as sleep disturbances, digestive problems, or chronic pain (1).

The precise cause of depression remains unknown, but it is believed to result from the interaction of various factors, including genetic factors, imbalances in brain chemistry, environmental stress, traumatic life events, and hormonal changes. Major depression can be managed with proper diagnosis and treatment. Treatment often involves a combination of psychotherapy (therapy) and/or antidepressant medication. A supportive environment, healthy lifestyle habits, exercise, regular sleep, and nutrition can also assist in managing depression (2).

The first-line medications for the treatment of depression, due to their advanced safety and tolerability profiles, are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and drugs that act on dopamine and other serotonin receptors. Monoamine oxidase inhibitors and tricyclic antidepressants are rarely used today. In cases of treatment resistance, there are a few medications with antidepressant properties that have evolved almost as much as antipsychotic and antiepileptic properties (such as quetiapine, ziprasidone, lamotrigine), but their use requires expertise. The use of antipsychotics as monotherapy in depression is not appropriate (3).

In recent years, numerous studies have been published evaluating the use of antipsychotic medications that are typically used in psychotic disorders for the treatment of depression. Antipsychotic drugs are commonly employed in the treatment of schizophrenia and other psychotic disorders. They achieve their antipsychotic effects by influencing dopamine receptors and regulating dopamine activity in the brain. Additionally, they can also affect serotonin receptors. Therefore, it makes sense to focus on the antidepressant effects of antipsychotics (4).

Antipsychotic drugs are divided into two main categories: typical (classical) antipsychotics and atypical (second-generation) antipsychotics. Typical antipsychotics are often referred to as older antipsychotics and include drugs such as chlorpromazine and haloperidol. Atypical antipsychotics, on the other hand, are newer-

generation drugs and include medications like risperidone, olanzapine, and clozapine (5).

Treatment-resistant major depression (TRD) is a term used when an individual does not show significant improvement or experiences a recurrence of symptoms despite one or more antidepressant medication treatments. When there is no response to depression treatment, the following questions should first be considered: Was the diagnosis accurately made? Are the remaining symptoms due to the underlying illness or are they side effects of the medications being used? Was the medication administered at the correct dosage and for the appropriate duration? Did the patient take the medication? Is there any interaction with other medications? Is there comorbidity with another mental illness? Is there a history of substance or alcohol use? If the patient is adhering to the prescribed treatment regimen, not using alcohol or substances, then a change in treatment may be necessary (6).

The approach to treatment-resistant major depression can be summarized as follows(7, 8):

1- Drug Treatment

- Antidepressant medication change: Trying a different antidepressant or combination of antidepressants may be considered. Combining different classes or mechanisms of antidepressants can enhance treatment response.
- Dosage adjustments: Increasing or decreasing medication doses may be effective in some cases.
- Medication combinations: Using two or more antidepressants together may be effective in some individuals with treatment-resistant depression. However, such combinations should be carefully managed and monitored by a specialist.

2- Psychotherapy

- Cognitive Behavioral Therapy (CBT): This type of therapy can be effective in managing depression symptoms and changing negative thought and behavior patterns. Longer-term or more intensive CBT programs are also accessible for individuals dealing with treatment-resistant depression.
- Psychodynamic therapy: This therapy aims to explore an individual's past experiences, relationships, and unconscious processes. In some cases, it may be effective for individuals with treatment-resistant depression.

3- Electroconvulsive Therapy (ECT):

- In some individuals with treatment-resistant major depression, ECT can be a treatment option used to rapidly alleviate symptoms. This method operates by inducing a neurological response through controlled electrical current application to the brain.

4- Transcranial Magnetic Stimulation (TMS):

- In this method, magnetic fields that target nerve cells in the brain are generated through a magnetic coil placed on the head. It can be effective in alleviating symptoms in some individuals with treatment-resistant depression.

In the last two decades, the use of atypical antipsychotics in the treatment of depression has rapidly increased worldwide. In a study conducted in 2007 and 2008, it was reported that approximately 3.7 million patients in the United States were prescribed atypical antipsychotic medications for depression each year (9).

When used at low doses as monotherapy, including aripiprazole, it appears that these atypical antipsychotic agents are not effective in reducing depressive symptoms. However, there have been limited studies on the use of low-dose atypical antipsychotics,

making it inappropriate to draw significant treatment effects from the limited data available (10).

In the case of Treatment-Resistant Depression (TRD), low-dose aripiprazole has demonstrated significant efficacy in terms of response and remission outcomes when compared to a placebo. Therefore, low-dose atypical antipsychotics could be a promising adjunctive agent for TRD and warrant further research. The incidence of serious side effects with atypical antipsychotic medications used at lower doses is lower, which increases tolerability and compliance (11-13).

The United States Food and Drug Administration (FDA) has approved the use of aripiprazole (daily 5-10 mg, maximum dosage 15 mg) as an adjunctive medication in the treatment of depressive disorders. Combination therapy with olanzapine and fluoxetine has also been approved by the FDA for the treatment of treatment-resistant depression (olanzapine daily 5-20 mg, fluoxetine 20-50 mg). Extended-release quetiapine (daily 150-300 mg) has also been approved by the FDA as an adjunctive treatment for depressive disorders. This is the only atypical antipsychotic approved for adjunctive treatment in depression in Europe and has been approved for both adjunctive and primary treatment in Australia (14).

1.1 Pharmacological Mechanisms of Antipsychotics in the Treatment of Depressive Disorders

The antidepressant effects of typical antipsychotics are believed to be associated with the inhibition of D2 and D3 receptors in the dopamine (DA) pathway in the prefrontal cortex, leading to an increase in dopamine levels in the prefrontal cortex. Other mechanisms considered among the antidepressant effects of atypical antipsychotics include reduced activation of dopamine receptors, reduced activation of 5-hydroxytryptamine 1A (5-HT1A) receptors, inhibition of 5-HT2A and 5-HT2C receptors, inhibition of alpha-2 receptors, blockade of norepinephrine transporter (NET), regulation of the glutamate or gamma-aminobutyric acid (GABA) system,

decreased cortisol levels, and changes in brain-derived neurotrophic factor (BDNF) levels (15, 16).

1.2 Use of Typical Antipsychotics in Depression

The use of typical antipsychotics such as haloperidol and chlorpromazine in the treatment of depression has a long history. However, the utilization of these conventional antipsychotics has declined due to an increased risk of extrapyramidal symptoms (EPS) like parkinsonism, dystonia, akathisia, and tardive dyskinesia (17). Additionally, their use has been discontinued because of their association with torsade's des pointes and sudden cardiac death (18).

With atypical antipsychotics, which are reported to have a lower incidence of EPS, therapeutic strategies have gained importance in the treatment of Treatment-Resistant Depression (TDD). Dopamine D2 receptors, the primary target in the brain for antipsychotics, have been found to play a role in the development of EPS. Typical antipsychotics have a higher affinity for binding to dopamine receptors and a shorter dissociation time. In contrast, atypical agents have a weaker affinity for D2 receptors and a longer dissociation time from dopamine. As a result, atypical agents temporarily occupy D2 receptors and then rapidly dissociate, allowing for normal dopamine neurotransmission. An occupancy rate of approximately 65% in D2 receptors is reported for effective antipsychotic action. However, when the occupancy rate of an antipsychotic exceeds 80% in D2 receptors, EPS induction occurs (19).

1.3. Use of Atypical Antipsychotics in Depression

1.3.1. Adding Clozapine to Treatment

Clozapine has been found effective in treatment-resistant schizophrenia patients, causing fewer extrapyramidal symptoms or tardive dyskinesia compared to typical antipsychotics and not elevating prolactin levels (20-22). It interacts with dopamine and serotonin receptors, suggesting antidepressant potential (23). In a study involving schizophrenia patients resistant to neuroleptics,

clozapine was shown to be effective in reducing suicidal ideation and suicide attempts (24); however, Sernyak et al. (25) did not find any significant difference in the rate of suicide or accidental death in a large cohort study of schizophrenia patients. Patients using this specific atypical agent carry a rare but significantly important risk of agranulocytosis, occurring in 1-2% of cases. Clozapine selectively affects precursors of polymorphonuclear leukocytes in the bone marrow and has other hematological effects such as leukopenia, neutropenia, and eosinophilia. In a meta-analysis comparing clozapine to other atypical antipsychotics for schizophrenia, clozapine showed a tendency towards more nausea, fatigue, excessive salivation, and orthostatic dizziness compared to other atypical agents. Considering the severity of side effects associated with clozapine, its use is limited to patients resistant or intolerant to other antipsychotic drugs (26).

1.3.2 Adding Olanzapine to Treatment

There is clinical evidence that the atypical antipsychotic olanzapine, when combined with fluoxetine, increases serotonin, norepinephrine, and dopamine levels in the rat brain (27). In rats given the combination of olanzapine and fluoxetine, norepinephrine and dopamine levels increased to 242% and 315% of baseline values, respectively, significantly higher than the levels produced by either agent alone. These increases in prefrontal norepinephrine and dopamine levels suggest a possible neurochemical basis for the synergistic antidepressant effect observed in clinical trials.

Randomized controlled studies of acute and long-term treatment with olanzapine alone or in combination with fluoxetine have yielded different results in the treatment of Treatment-Resistant Depression (TDD). Thase et al. (28) conducted two separate randomized controlled studies comparing olanzapine monotherapy, fluoxetine monotherapy, and olanzapine/fluoxetine combination therapy. In the first study, there were no statistically significant differences in remission rates and response rates among the three treatment options. The second study, however, demonstrated that the

olanzapine/fluoxetine combination was significantly more effective than the other groups. When both studies were combined, it became evident that the olanzapine/fluoxetine combination differed significantly from both monotherapies.

Shelton et al. (29) found that olanzapine/fluoxetine combination therapy was more effective than both monotherapies; however, another study evaluated the same groups and found no significant difference between therapies at the end of treatment. Studies conducted in patients with Treatment-Resistant Depression (TDD) who had acute and long-term treatment resistance have shown that olanzapine/fluoxetine combination therapy exhibited a rapid, potent, and sustained antidepressant effect and demonstrated a similar safety profile compared to component monotherapies. At the end of treatment, there was no significant difference between the olanzapine/fluoxetine combination and olanzapine or fluoxetine monotherapies; however, the onset of action of olanzapine/fluoxetine treatment may influence clinical treatment strategies. For example, the speed of antidepressant efficacy could be a crucial factor in treatment selection, especially in patients with suicidal ideation (30, 31). In conclusion, based on the existing studies, adding olanzapine to treatment appears to expedite the response time to treatment, at the very least.

1.3.3 Adding Aripiprazole to Treatment

Studies have been published reporting that aripiprazole is effective in the treatment of depressive symptoms in patients with schizophrenia and bipolar disorder (32, 33). The pharmacological effect of aripiprazole is associated with its partial agonist activity at D2, D3 and 5-HT1A receptors, as well as its antagonistic effect at 5-HT2A receptors (34-36).

The addition of aripiprazole to SSRIs in the treatment of Treatment-Resistant Depression (TDD) has been found to be effective in numerous randomized, double-blind, placebo-controlled studies (37, 38). The addition of aripiprazole has led to rapid improvements in Montgomery-Åsberg Depression Rating Scale

(MADRS) total scores, with improvement starting in the first and second weeks of treatment and continuing throughout the treatment duration. In cases where aripiprazole was added, significantly higher rates of remission and response compared to placebo were observed at the endpoint of usually 8-week studies. Berman et al. (34) also demonstrated that the remission rate was twice as high in patients where aripiprazole was added to antidepressants compared to placebo.

The addition of aripiprazole to treatment has been well-tolerated in studies. Completion rates with aripiprazole until the end of treatment were found to be high, and discontinuation rates due to side effects were similar to placebo groups. Among the most common adverse events associated with aripiprazole are akathisia, headache, fatigue, sleep disturbances, tremor, constipation, and restlessness. Aripiprazole has been associated with greater weight gain compared to placebo in some studies, but findings are inconsistent. In one study, a significant increase in weight gain was observed in the aripiprazole-added group compared to placebo (+ 2.01 ± 0.17 kg vs. + 0.34 ± 0.18 kg; $p < 0.001$; + 1.47 ± 0.16 kg vs. 0.42 ± 0.17 kg; $p < 0.001$) (39). In contrast, Berman, and colleagues (34) found no significant difference in weight gain between the aripiprazole-added group and placebo (+ 1.2 kg vs. + 0.8 kg; $p = 0.14$).

Evidence suggests that the addition of aripiprazole does not have adverse effects on prolactin levels, and it is believed that adding aripiprazole does not worsen the potential for hyperprolactinemia (39, 40). Furthermore, improvements in sexual function are more pronounced compared to placebo. Considering the higher response and remission rates, as well as its well-tolerated safety profile in studies, the addition of aripiprazole to treatment appears to be one of the most important antipsychotics that can be used in TDD (41, 42).

1.3.4 Adding Quetiapine to Treatment

Quetiapine has been approved by the U.S. Food and Drug Administration (FDA) for schizophrenia, major depressive disorder

(MDD), and manic episodes and depression associated with bipolar disorder (43). Its pharmacological effects are similar to the first atypical antipsychotic, clozapine, and it antagonizes a wide range of receptors, including serotonergic (5-HT1A and 5-HT2A), dopaminergic (D1 and D2), histaminergic (H1), and adrenergic (α1 and α2) receptors (44). Additionally, it has been reported that one of quetiapine's main active metabolites, norketiapine, blocks the human norepinephrine transporter (NET), inhibits norepinephrine reuptake, and has a high binding affinity to 5-HT1A, H1, and α1 receptors (45).

A randomized, single-blind, placebo-controlled study was conducted with patients suffering from major depression and associated anxiety. These patients were treated with either paroxetine and placebo or paroxetine and quetiapine. After eight weeks, the authors reported significantly reduced "Hamilton Depression Rating Scale (HAM-D)" scores in the combination therapy group compared to the placebo group ($P < 0.008$). In terms of anxiety, "Hamilton Anxiety Rating Scale (HAM-A)" scores showed significant improvement with quetiapine ($p < 0.008$) (46).

In another randomized, double-blind, placebo-controlled study, researchers investigated the treatment of MDD and the maintenance of symptom remission in 72 MDD patients. The study compared four groups: paroxetine monotherapy, venlafaxine monotherapy, paroxetine and quetiapine combination therapy, and venlafaxine and quetiapine combination therapy. Overall, they found that improvement in depressive symptoms and the development of remission occurred most frequently in the paroxetine and quetiapine group, followed by the venlafaxine and quetiapine group, and then during paroxetine monotherapy and venlafaxine monotherapy (47).

In a six-week randomized, double-blind, placebo-controlled study, ketiapin was added to patients with major depressive disorder at different doses (150 and 300 mg/day). Both groups with ketiapin added at the two doses showed significant improvement in depressive symptoms measured by the Montgomery-Åsberg

Depression Rating Scale (MADRS) and HAM-D total scores. Significant improvement in MADRS was observed for both ketiapin doses in the first week (48). However, El-Khalili et al. (49), in their eight-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study, reported that only the group with 300 mg/day ketiapin added showed significant symptom improvement (MADRS) from the first week, while the group with 150 mg/day ketiapin added showed only transient benefit in the first week, which then diminished. In conclusion, it would be accurate to say that adding 300 mg/day ketiapin may be more effective than 150 mg/day in patients with treatment-resistant major depressive disorder and a high recurrence rate of MDD.

Bauer and colleagues (48) reported a positive relationship between the use of quetiapine and sleep quality. They found a beneficial effect on sleep quality in patients receiving ongoing antidepressant treatments with the addition of quetiapine, as measured by the HAM-D sleep disturbance item and the Pittsburgh Sleep Quality Index (PSQI) scores. Gedge and colleagues (50) also supported the impact of quetiapine on changes in sleep quality in patients with treatment-resistant major depressive disorder.

1.3.5 Adding Risperidone to Treatment

Risperidone, developed from the typical antipsychotic haloperidol, possesses the ability to bind to serotonin (5-HT2) and dopamine (D2) receptors in the brain. According to Lakoski and colleagues (51), risperidone's antagonist effect on 5-HT2 receptors enhances the serotonergic effects of SSRIs on 5-HT2 receptors. In contrast to traditional antipsychotics, especially at low doses, risperidone antagonizes 5-HT2 receptors approximately 1,000 times more than D2 receptors (52). Given that occupancy of over 80% of D2 receptors triggers increased rates of EPS and tardive dyskinesia development, adjunct therapy with low-dose risperidone is a more preferable option in terms of safety profile (53). Furthermore, several studies have recommended risperidone as the primary adjunct agent due to its comparative non-sedative nature and lack of

disruption in glucose metabolism associated with weight gain or diabetes (54).

In a double-blind, crossover study, the addition of risperidone showed a significant reduction in HAM-D ($p = 0.04$) and Beck Depression Inventory (BDI) ($p = 0.02$) scores. Significant improvements in REM sleep, stage 2 sleep, and sleep wakefulness, positively correlated with a decrease in HAM-D scores, were reported in the risperidone addition group after just two weeks. These data support the antagonist profile of risperidone, which is associated with enhancing serotonin and norepinephrine neurotransmission through the blockade of 5-HT2 and D2 receptors (55).

In another study, the addition of risperidone demonstrated a significant improvement in depressive symptoms (56). In this study, patients who had an inadequate response to citalopram monotherapy were started on risperidone. Responding patients then entered the long-term phase, either continuing risperidone or switching to the placebo group. It was shown to reduce depressive symptoms in the short and long term (57).

There are also numerous studies and case reports supporting the benefits of adding low-dose risperidone in depression. In patients who did not respond to at least two or more SSRI trials, the addition of low-dose risperidone resulted in a rapid improvement in mood and anxiety symptoms in less than one week. This improvement was observed in sleep quality, impulse control, sexual dysfunction, agitation, response rates, and remission rates (58-60).

In summary, the 5-HT2 antagonist properties of risperidone enhance the extracellular monoamine levels, which may be one of the reasons why atypical antipsychotics like risperidone can be beneficial in patients with treatment-resistant major depressive disorder.

1.3.6 Adding Ziprasidone to Treatment

There is also evidence showing that the addition of ziprasidone to treatment can enhance the effects of antidepressant therapy in treatment-resistant patients. In an open-label randomized study conducted on individuals with treatment-resistant depression who were using a high dose of sertraline, patients receiving adjunctive therapy with ziprasidone at a dose of 160 mg/day achieved better scores on the Clinical Global Impression-Severity (CGI-S) scale compared to those receiving ziprasidone as an adjunct to treatment. However, since this was a study with a small sample size, these results need to be confirmed (61). A retrospective study also found ziprasidone to be effective for treatment-resistant depression, but there was no significant difference in efficacy between ziprasidone and other atypical antipsychotics (62). There is no randomized controlled study in the literature regarding the benefit of other antipsychotics as adjunctive therapy in the management of depressed patients.

Research conducted in recent years shows that antipsychotic drugs have antidepressant effects. These effects are often more pronounced in second-generation (atypical) antipsychotics. Their antidepressant effects are associated with the modulation of dopamine and serotonin receptors. Antipsychotics can help alleviate depression symptoms by regulating serotonin and dopamine levels in the brain. However, in the long term, their use can lead to increased costs and side effects (such as weight gain, elevated prolactin levels, extrapyramidal side effects, etc.) compared to placebo, which may affect patient adherence, leading to higher discontinuation rates in groups where atypical antipsychotics are added to the treatment (63, 64). Therefore, these medications should be added to the treatment of cases with treatment-resistant major depression with caution and close monitoring. In the context of patient-centered care, atypical antipsychotic agents can be added to the treatment in cases of treatment-resistant depression or to enhance treatment.

References

1. Belmaker RH, Agam G. Major depressive disorder. New England Journal of Medicine. 2008;358(1):55-68.

2. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nature reviews Disease primers. 2016;2(1):1-20.

3. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? Journal of Clinical Psychiatry. 2003;64(2):123-33.

4. Mulder R, Hamilton A, Irwin L, Boyce P, Morris G, Porter RJ, et al. Treating depression with adjunctive antipsychotics. Bipolar disorders. 2018;20:17-24.

5. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Archives of general psychiatry. 2003;60(6):553-64.

6. Berlim MT, Turecki G. Definition, assessment, and staging of treatment—resistant refractory major depression: a review of current concepts and methods. The Canadian Journal of Psychiatry. 2007;52(1):46-54.

7. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. American Journal of Psychiatry. 2001;158(1):131-4.

8. Nelson JC. Managing treatment-resistant major depression. Journal of Clinical Psychiatry. 2003;64(1):5-12.

9. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. Pharmacoepidemiology and drug safety. 2011;20(2):177-84.

10. Barnes SA, Lindborg SR, Seaman Jr JW. Multiple imputation techniques in small sample clinical trials. Statistics in medicine. 2006;25(2):233-45.

11. Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. Journal of Clinical Psychiatry. 2009;70(4):540.

12. Hicks P, Hicks XP, Meyer H, Shisslak C. How best to manage treatment-resistant depression? Should you augment the treatment regimen with lithium, thyroxin, or an atypical antipsychotic? This review will help you decide. Journal of Family Practice. 2010;59(9):490-6.

13. Taylor D. Low dose typical antipsychotics–a brief evaluation. Psychiatric Bulletin. 2000;24(12):465-8.

14. Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. Journal of Managed Care Pharmacy. 2012;18(5 Supp B):1-20.

15. Šagud M, Mihaljević-Peleš A, Begić D, Vuksan-Ćusa B, Kramarić M, Živković M, et al. Antipsychotics as antidepressants: what is the mechanism? Psychiatria Danubina. 2011;23(3.):302-7.

16. Rogóż Z. Combined treatment with atypical antipsychotics and antidepressants in treatment-resistant depression: preclinical and clinical efficacy. Pharmacological Reports. 2013;65(6):1535-44.

17. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry. 2009;166(9):980-91.

18. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. New England journal of medicine. 2009;360(3):225-35.

19. Seeman P. Atypical antipsychotics: mechanism of action. The Canadian Journal of Psychiatry. 2002;47(1):27-38.

20. CLAGHORN J, HONIGFELD G, ABUZZAHAB SR FS, WANG R, STEINBOOK R, TUASON V, et al. The risks and benefits of clozapine versus chlorpromazine. Journal of clinical psychopharmacology. 1987;7(6):377-84.

21. Lieberman JA, Safferman AZ, Pollack S, Szymanski S, Johns C, Howard A, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. American Journal of Psychiatry. 1994;151(12):1744-52.

22. Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis--incidence and risk factors in the United States. New England Journal of Medicine. 1993;329(3):162-7.

23. Chandrasekaran P. Agranulocytosis monitoring with clozapine patients: to follow guidelines or to attempt therapeutic controversies? Singapore medical journal. 2008;49(2):96-9.

24. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. The American journal of psychiatry. 1995.

25. Sernyak MJ, Desai R, Stolar M, Rosenheck R. Impact of clozapine on completed suicide. American Journal of Psychiatry. 2001;158(6):931-7.

26. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophrenia research. 2002;56(1-2):1-10.

27. Zhang W, Perry KW, Wong DT, Potts BD, Bao J, Tollefson GD, et al. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2000;23(3):250-62.

28. Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. The Journal of clinical psychiatry. 2007;68(2):224-36.

29. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry. 2001;158(1):131-4.

30. Shelton RC, Williamson DJ, Corya SA, Sanger TM, Van Campen LE, Case M, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. The Journal of clinical psychiatry. 2005;66(10):1289-97.

31. Corya SA, Andersen SW, Detke HC, Kelly LS, Van Campen LE, Sanger TM, et al. Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study. The Journal of clinical psychiatry. 2003;64(11):1349-56.

32. Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. International Journal of Neuropsychopharmacology. 2003;6(4):325-37.

33. Vieta E, Bourin M, Sanchez R, Marcus R, Stock E, McQuade R, et al. Effectiveness of aripiprazole v. haloperidol in

acute bipolar mania: double-blind, randomised, comparative 12-week trial. The British Journal of Psychiatry. 2005;187(3):235-42.

34. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 2007;68(6):843-53.

35. Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. Journal of Pharmacology and Experimental Therapeutics. 2002;302(1):381-9.

36. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. European journal of pharmacology. 2002;441(3):137-40.

37. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS spectrums. 2009;14(4):197-206.

38. Sheffrin M, Driscoll HC, Lenze EJ, Mulsant BH, Pollock BG, Miller MD, et al. Pilot study of augmentation with aripiprazole for incomplete response in late-life depression: getting to remission. Journal of Clinical Psychiatry. 2009;70(2):208.

39. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. Journal of clinical psychopharmacology. 2008;28(2):156-65.

40. Papakostas GI, Miller KK, Petersen T, Sklarsky KG, Hilliker SE, Klibanski A, et al. Serum prolactin levels among outpatients with major depressive disorder during the acute phase of

treatment with fluoxetine. Journal of Clinical Psychiatry. 2006;67(6):952-7.

41. Van Londen L, Molenaar R, Goekoop J, Zwinderman A, Rooijmans H. Three-to 5-year prospective follow-up of outcome in major depression. Psychological Medicine. 1998;28(3):731-5.

42. Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Archives of general psychiatry. 2000;57(4):375-80.

43. Cheer SM, Wagstaff AJ. Quetiapine. A review of its use in the management of schizophrenia. CNS drugs. 2004;18(3):173-99.

44. Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. The Journal of clinical psychiatry. 2002;63 Suppl 13:5-11.

45. Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB, Roth BL. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2008;33(10):2303-12.

46. Yargic LI, Corapcioglu A, Kocabasoglu N, Erdogan A, Koroglu G, Yilmaz D. A prospective randomized single-blind, multicenter trial comparing the efficacy and safety of paroxetine with and without quetiapine therapy in depression associated with anxiety. International journal of psychiatry in clinical practice. 2004;8(4):205-11.

47. Hussain M, Waheed W, Hussain S, Chaudhry Z, editors. A comparison of unipolar depression treatment using antidepressants alone versus using antidepressants in combination with quetiapine. European Neuropsychopharmacology; 2005:

ELSEVIER SCIENCE BV PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.

48. Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. The Journal of clinical psychiatry. 2009;70(4):540-9.

49. El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. The international journal of neuropsychopharmacology. 2010;13(7):917-32.

50. Gedge L, Lazowski L, Murray D, Jokic R, Milev R. Effects of quetiapine on sleep architecture in patients with unipolar or bipolar depression. Neuropsychiatric Disease and Treatment. 2010:501-8.

51. Lakoski JM, Aghajanian GK. Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. Neuropharmacology. 1985;24(4):265-73.

52. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacology bulletin. 1992;28(2):213-8.

53. Seeman P. Atypical antipsychotics: mechanism of action. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2002;47(1):27-38.

54. Viner M, Schroeder S, Kamper P. A practical classification of current atypical antipsychotics. Primary Psychiatry. 2000;7(9):84-8.

55. Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijsman HJ, Cowen PJ. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. The Journal of clinical psychiatry. 2003;64(2):192-6.

56. Gharabawi G, Canuso C, Pandina G, Bossie C, Kujawa M, Kosik-Gonzalez C, et al., editors. Risperidone treatment of resistant depression: a double-blind randomized trial. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology; 2006: NATURE PUBLISHING GROUP MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.

57. Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2006;31(11):2505-13.

58. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. The Journal of clinical psychiatry. 1999;60(4):256-9.

59. O'Connor M, Silver H. Adding risperidone to selective serotonin reuptake inhibitor improves chronic depression. J Clin Psychopharmacol. 1998;18(1):89-91.

60. Viner MW, Chen Y, Bakshi I, Kamper P. Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. J Clin Psychopharmacol. 2003;23(1):104-6.

61. Dunner DL, Amsterdam JD, Shelton RC, Loebel A, Romano SJ. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. The Journal of clinical psychiatry. 2007;68(7):1071-7.

62. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. The Journal of clinical psychiatry. 2004;65(7):975-81.

63. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry. 2009;166(9):980-91.

64. Dilbaz N, Çavus SY. Depresyon tedavisinde yetersiz yanit durumunda güçlendirme tedavileri. Psychiatry and Clinical Psychopharmacology. 2010;20:S4.

CHAPTER V

Overview Of the Effects of Screen Exposure on Children

Erdal SARI[1]

Introduction

The increasing use of information technology has led to the integration of electronic media devices, such as televisions, computers, smartphones, and tablets, into people's daily routines for purposes of work, education, and entertainment (Duch et al., 2013, Paudel et al., 2017). While television remains the predominant form of screen-based activity for children, the utilization of other devices such as computers, video games, tablets, and smartphones is also declining among younger age groups. What is even more remarkable is the significant surge in the utilization of such gadgets by extremely young children and even infants. This increased use reflects the increasing use of screen media by both families and society, and the

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increasing marketing of television channels, digital devices and applications to young children (Vaala, Ly & Levine, 2015). Screen time has become increasingly intricate in recent years due to the proliferation of electronic media devices worldwide. Over the last 20 years, the daily time children are exposed to screen-based devices has increased, while the initial exposure has gradually become smaller (Dumuid, 2020).

In addition to the advantages of access to information and rapid communication, many studies have been conducted in recent years regarding the physical health and psychological problems that can be observed among infants, children and adolescents regarding screen exposure. Excessive screen time in early childhood, when the brain is highly plastic, can disrupt the development of brain structure. A study conducted in 2019 discovered evidence, through magnetic resonance imaging (MRI), of negative associations between the structural integrity of white matter pathways and the amount of time children aged 3 to 5 years spend using screens (Hutton et al., 2019). Excessive screen time, particularly television viewing, can impede the progress of physical and cognitive skills and contribute to issues such as obesity, sleep disturbances, depression, and anxiety. The user is requesting information about the physiological mechanisms that cause negative health effects associated with screen time, as well as the impact of various types of screen and media content on specific health outcomes. Their contributions lack clarity. The detrimental health effects of screen exposure are an escalating public health concern. A nationwide survey, which accurately represents the United States, discovered that 68% of children below the age of 2 engage with screen-based devices on an average day and a recent survey conducted in Italy revealed that 80% of children aged 3 to 5 engage with screen-based devices on a daily basis (Duch et al., 2013). It shows that 100,000 people use their parents' smartphones (Bozzola et al., 2018). Despite the potential benefits of media time, excessive or inappropriate use of technology has a significant impact on children's development and health (Domingues-Montanari, 2017). There is a relationship

between increased screen time and physical and mental health problems and negative consequences on cognitive, language, social and emotional development. It is recommended by the American Academy of Pediatrics that the time spent in front of the screen in early childhood should be no more than one hour per day (Table 1).

Table 1 Guidelines from the American Academy of Pediatrics on screen time

-Children under 18 months; Screen use should be avoided except for video calls.
-18-24 months; Selected high-quality content should be selected and watched under parental supervision only. Media use on their own should be avoided.
-Ages over 2 years old; Access to selected content should be provided without exceeding 1 hour a day, together. Watching /playing and screen-free activities should be encouraged.
-Older children- adolescents; Adequate sleep (8-12 hours), physical activity (1 hour), and screen-free time should be provided. There should be no screen devices in bedrooms and screens should be turned off before sleeping.

Parents should create personal media plans for their children, and these plans should be appropriate to the child's age, needs and development. The plan should also be shared with caregivers and grandparents and compliance with the plan should be ensured (American Academy of Pediatrics, 2016). The physical and psychological negative effects of screen exposure on children are shown in Table 2.

Table 2: Problems Caused by Excessive Screen Exposure

Physical Problems	Social/Psychological Problems
Musculoskeletal system disorders Eye disorders Obesity Cardiovascular disorders Headache – migraine Increased frequency of epilepsy/seizures	Attention disorders, Aggressive behavior Sleep problems Autism Speech disorders Cyber bullying, Exploitation

Physical Disorders

Musculoskeletal System Disorders

A sedentary lifestyle or lack of exercise while sitting all the time can cause significant orthopedic effects. Screen time, primarily on small screen handheld devices, affects posture, creating musculoskeletal burden and discomfort symptoms. These symptoms are a result of intense repetitive wrist and arm movement and head tilt, often seen while playing video games (Lui, Szeto & Jones, 2011). Neck pain is a multifaceted and significant public health issue in contemporary societies. Neck pain is ranked 8th among other prominent health issues affecting adolescents, according to the Global Burden of Disease report by the World Health Organization (WHO) (IHME HealthData, 2016). Evidence suggests that children and adolescents who consistently experience pain are at a higher risk of developing chronic pain in adulthood. In recent years, a growing number of data reports have contributed to the recognition of "text neck syndrome," a condition that can be regarded as a syndrome of

the 21st century. This clinical condition, known as cervical spinal degeneration, occurs due to the repetitive strain caused by frequent forward bending while using mobile devices and engaging in prolonged texting (Fares, Fares & Fares, 2017, TEXT NECK, 2016). Children and adolescents are believed to spend an average of 5 to 7 hours per day in a forward head posture while reading and texting on their smartphones and handheld devices. The combined impact of this exposure has been documented to lead to concerning outcomes of excessive strain on the cervical spine area, typically ranging from 1825 to 2555 hours annually (Hansraj, 2014). Hence, it is crucial to conduct screenings on children who are at a heightened risk in order to promptly identify and provide treatment during their childhood. 'Text neck' refers to the condition caused by the prolonged and repetitive bending of the neck while using electronic devices such as smartphones or tablets. When it comes to syndrome, it is crucial to take measures to avoid its occurrence. When utilizing smartphones or other handheld devices, it is important to consider the following recommendations:

1. Refrain from excessive use and ensure regular intervals of rest.

2. Minimize prolonged periods of immobile positions.

3. Orient the device in a manner that minimizes strain on the head/neck and upper limbs.

4. Refrain from engaging in repetitive actions, such as extended periods of typing or scrolling.

5. Refrain from prolonged one-handed holding of bulky or weighty devices (Toh et al., 2017).

Eye Disorders

Prolonged computer screen exposure can lead to ocular fatigue, impaired visual acuity, ocular dryness, cephalalgia, and physical discomfort. These symptoms could arise due to factors such as glare, inadequate lighting, or incorrect imaging settings (Akinbinu

& Mashalla, 2014). Varma and colleagues, the prevalence of childhood myopia in the United States has increased by over 100% in the past fifty years, as demonstrated by the Many Ethnic Pediatric Eye Disease Studies (MEPEDS) that investigated the causes of ocular disease (Varma et al., 2016). Problems begin when the human eye, which has evolved to see long distances in 3D, suddenly focuses on a bright object 10-50 cm away all day long.

Digital eye strain (DES): Long time screen use of during/after emerge coming out complaints expression it does. Symptoms; eyelash fatigue, eye pain, burning, pity, itching, foreign object feeling, irritation feeling, eye dryness, cloudy sight, couple sight, eye tearing, photophobia and head-neck pain shaped it could be.

Risk factors:

- Uncorrected refractive error (refraction error) - including presbyopia
- accommodation disorders
- Blink less frequently
- intense light
- Close distance
- small print

Suggestions:

- After 20 minutes of screen time, you should look away from the view for at least 20 seconds without focusing on a nearby object.
- The screen should be placed correctly, it should be positioned at arm's length by correcting the viewing angle, it should be kept at eye level or slightly lower, and larger fonts should be used for texts.
- The amount of light must be adjusted; Too much or too little light increases the complaints. Backlight and appropriate lighting should be used while reading.
- We blink less when using a screen for a long time; Artificial eye drops should be used for dry eyes.

- The right glasses should be used and filtered glasses and lenses should be preferred.
- Must use a screen filter.

Obesity and Cardiovascular Disorders:

Although there is insufficient evidence for a relationship between screen time and body mass index in very young children, many studies suggest that the risks of being overweight posed by early screen use may persist into later life. In the early years, watching television may become routine, putting children who are heavy viewers at risk of being sedentary and overweight (Courage & Setliff, 2010). A study conducted in Canada in 2012 showed that children who watched TV for only 1 hour a day were 50% more likely to be overweight than those who watched less (Shenouda & Timmons, 2012). While television viewing reinforces sedentary behaviors, it also exposes children to advertisements for unhealthy foods and encourages snacking, which increases overall food intake (Mulligan et al., 2011).

Possible causes of obesity due to spending long periods in front of the screen:

-Decreased physical activities

-Unhealthy eating habits

-Increased cortisol level with sympathetic stimulation, disrupted sleep patterns, decrease in sleep duration and decreased melatonin result; increase in blood pressure, decrease in HDL level, increase in LDL level and insulin resistance.

-Decreased bone density

The first approach that comes to mind when explaining the obesity epidemic of our age is the decrease in time spent with physical activities; but this alone is not enough. Screen time also indirectly affects food intake, leading to obesity. There is a significant relationship between each extra hour spent in front of a

screen and an increase in poor eating habits; sugary drinks, chocolate/wafer, biscuit-cake, chips, pizza-hamburger etc. Despite the increase in consumption, there is a decrease in vegetable consumption, and exposure to advertisements for foods with high sugar/fat content also contributes to this type of nutrition. For over three decades, evidence has been reported regarding negative health outcomes associated with TV viewing about sitting time. With technological progress and the introduction of these computers and video games into our lives, studies on-screen exposure times are increasing (Biddle, Garcia Bengoechea & Wiesner, 2017). There is a claim that engaging in sedentary activities while sitting in front of a screen can raise the likelihood of developing obesity, HDL dysfunction, and high blood pressure. These factors are known to significantly increase the risk of cardiovascular diseases (Goldfield et al., 2011, Sharma, Merghani & Mont, 2015). Chronic sympathetic stimulation poses a risk for cardiovascular diseases (Curtis & O'Keefe, 2002). There is a higher level of sympathetic arousal in school-age children and young adults with internet addiction behavior (Hsieh & Hsiao, 2016), and high sympathetic arousal may be a partial cause of sleep disruption. The exact mechanisms by which inadequate sleep duration increases obesity are not clear enough. As a behavioral hypothesis; While less sleep is evaluated as more time to eat and the endocrine mechanisms; The relationships between hormone pathways such as insulin, cortisol, Ghrelin and leptin are discussed. During short sleep periods, the appetite-reducing hormone leptin is secreted less, while the appetite-increasing hormone Ghrelin increases.

Headache:

The incidence of headaches in children is increasing. Risk factors include low physical activity, obesity, and insufficient sleep (Straube et al., 2013). There are studies reporting a positive relationship between headache and increased screen time, and a significant relationship between headache relief as screen time decreases (Falkenberg Johansen & Thorud, 2020, Hrafnkelsdottir et

al., 2018). It is not clear whether screen exposure causes migraines. Publications are stating that they are related, although they are few (Attygalle, Hewawitharana & Wijesinghe, 2020). A significant relationship is evident between the increase in complaints and screen time in children with migraine (Lund, Berring-Uldum & Colak, 2021). Excessive screen use should also be questioned in all children presenting with primary headaches. It is recommended to limit screen time in children diagnosed with migraine before starting drug treatment (Çaksen, 2021).

Epilepsy and Screen:

Although visually evoked seizures have been known for a long time, new technologies used in television and games have led to an increase in such seizures. Rapidly changing bright screens are the most common trigger for photosensitive epilepsy. The first publication about video games was in 1981, reporting "space-invader epilepsy". After that a lot of case notifications have occurred (Bureau, Hirsch & Vigevano, 2004). There are many reports of seizures not only in photosensitive epilepsy but also in non-photosensitive epilepsy. A distance of more than 2 meters from the screen is safer and 100- Hz screens are less provocative. Recently, increased compliance with warnings by well-known video game manufacturers has resulted in a decrease in seizures.

Radiation:

With the increasing use of wireless devices by children, there is a growing concern about their potential susceptibility to radiofrequency electromagnetic radiation (RF-EMR) fields. Children are deemed to be more susceptible to RF-EMR fields due to the heightened sensitivity of their developing nervous systems. Moreover, their brain tissue exhibits higher conductivity, enabling a more significant penetration of RF-EMR in proportion to the size of their head. There is a claim that engaging in sedentary activities while sitting in front of a screen can raise the likelihood of developing obesity, HDL dysfunction, and high blood pressure.

These conditions are significant risk factors for cardiovascular morbidity.

Social/Psychological Problems

' Nomophobia ' is an abbreviation of the words **no – mobile-phobia**. It is the state of fear and anxiety observed in individuals when they do not have a phone. It is not a phobia; it is a withdrawal symptom of smartphone addiction. Problems that may occur due to screen addiction:

- Attention disorders
- Autism
- Sleeping disorders
- Speech disorders
- Depression
- Internet gaming disorder

Attention Deficit/Hyperactivity Disorder (ADHD):

It is a neurodevelopmental disorder characterized by early-onset inattention and hyperactivity/impulsivity symptoms in childhood and adolescence. Exposure to screens poses a potential risk for developing ADHD. Children in the general population may consistently exhibit a range of symptoms associated with ADHD, including difficulties with attention, hyperactivity, and impulsivity. This behavior is referred to as ADHD-related behavior and is linked to the amount of time spent using screens, such as watching TV and playing video games (Nikkelen et al., 2014). Excessive screen time (>2 hours) in preschool is associated with poor attention problems. The screen time-behavioral disorder relationship is more meaningful than all other risk factors (such as sleep, parental problems, socioeconomic problems, etc.). Studies conducted on ADHD show that even preschool children with the diagnosis spend much more screen time than the 1 hour/day recommended for them (Tamana et al, 2019, Tan & Zhou, 2022, Biçer, 2020). These findings show the

importance of the preschool period in informing and supporting families to limit screen time and increase physical activities.

Sleeping disorders:

Sleep is very important for the neurodevelopment of babies and young children. Research indicates that inadequate sleep, in terms of both length and quality, can pose a risk to the physical and mental well-being, as well as the psychosocial functioning, of children and young individuals. Approximately 20-30% of young children in Britain encounter sleep difficulties (Cheung et al., 2017). Time spent watching screens before bed is associated with an increase in sleep problems in this age group. The presence of any electronic device in a bedroom has been associated with fewer minutes of sleep per night, in part due to melatonin suppression.

Autism:

A lower age of onset for screen exposure, daily screen time, and cumulative screen exposure from birth is associated with the presence of autism-like behaviors in preschool. The first 3 years of age are the most sensitive period in this respect (Dong et al., 2021). There is a strong association between longer screen time by age 1 and autism spectrum disorder at age 3 (Kushima et al., 2022). Screen exposure during infancy, a period of rapid development, may be one of the acquired factors associated with the development of autism spectrum disorder. Compared to children with typical development, children with autism have longer screen time, and as the screen time increases in these children, the symptoms that occur also increase. Developmental delay becomes more evident at younger ages, especially as the time spent on the screen increases in these children, especially in language development.

Depression:

Depression is a growing public health concern and is increasingly prevalent among adolescents. Research has established

a correlation between the total amount of time spent using screens and the occurrence of depression and suicidal tendencies in teenagers (Maras et al., 2015). Liu et al. found a non-linear dose-response relationship between depressive symptoms and total screen time among children aged 5-18 who used digital media for more than two hours a day (Liu, Wu & Yao, 2016).

Addictive Screen Time Behavior:

The scholarly discourse pertaining to digital media research on addictive behavior has predominantly centered around internet usage and video games. However, the growing prevalence of app and messaging usage, particularly on mobile devices, can also contribute to the development of addictive behavior. While boys show video game addiction, it has been found that girls' addictive behavior focuses primarily on social networks (Schou Andreassen et al., 2016). Violent behavior is rarely the result of a single cause and is likely the result of the long-term influence of multiple factors. Out of all the risk factors, being exposed to aggressive behavior during childhood is the most accurate indicator of violent behavior during older adolescence and adulthood. Extensive research spanning several decades demonstrates that being exposed to violent content on television and video games raises the likelihood of engaging in violent behavior in the future, similar to the effect of growing up in an environment characterized by real-life violence (Anderson et al., 2017).

Internet gaming disorder (IGD):

Has been included in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) — Internet gaming disorder. Although there is no diagnostic code yet, it can be defined as persistent and recurrent internet use that is significant enough to cause anxiety and stress, mostly to enter games with other players. Its symptoms are similar to non-drug addictions. The presence of 5 out of 9 criteria in the last 12 months is diagnostic:

1-The mind is constantly occupied with the game: constantly thinking about the previous stages and next moves of the game and the game becoming the dominant activity in daily life.

2-Deprivation; sadness, anxiety, uneasiness, etc. when you cannot enter the game

3-Tolerance; spending more and more time in the game

4-Attempts to reduce or stop playing

5-Decrease in previous hobbies and other pastimes in real-life relationships outside of gaming

6-Continuing to play excessively despite knowing psychosocial problems

Do not lie to family members, doctors, etc. about gaming addiction

8- Taking refuge in games to get out of a negative mood

9- Academic success, family, work, etc., opportunities, achievements, etc., loss due to play.

Conclusion

The increase in the number of digital media devices is expanding, and the progression of digital media provides users with a more dynamic and rapidly evolving digital landscape. Children and adolescents appear to be adapting seamlessly to new technologies, yet a growing body of literature links excessive screen time to physical, psychological, social, and neurological negative health outcomes. In order to promote the well-being and growth of children in the era of technology, it is imperative for medical professionals and other healthcare providers to offer guidance to parents and caregivers regarding the suitable utilization of screen time:

- It is advisable to reduce the amount of time spent using screens.

-Screen time is not recommended for children under 2 years old.

-For children aged 2 to 5, routine screen time should be limited to less than 1 hour per day.

- Ensure that children under 5 years old do not have regular sedentary screen time as part of their child care routine.

- It is important to establish regular periods of time without screens on a daily basis, particularly during family meals and when sharing books.

-Given their melatonin-suppressing potential, screens should be avoided at least 1 hour before bedtime.

-When using screens, children should be together whenever possible.

-Ensure that the programming you choose is educational, suitable for the intended age group, and encourages active participation.

-As a family, attention should be paid to the use of screen time:

-Conduct a self-assessment of current screen habits and develop a family media plan for when, how, and where screens can (and cannot) be used.

-Help children recognize and question advertising messages, stereotypes and other problematic content.

-Adults should model healthy screen use.

-Settle for wholesome alternatives such as engaging in reading, participating in outdoor play, and indulging in creative, tactile activities.

- Shut down electronic devices within the household during designated periods of family interaction.

- Shut down electronic displays when not actively utilizing them and refrain from having a television playing in the background.

It should not be forgotten that too much screen time means missed opportunities for teaching and learning. There is no evidence to support the introduction of technology at an early age.

Consequently, there is a rise in the number of digital media devices available, and children and adolescents are easily adjusting to new technologies. However, a growing body of literature links excessive screen time to various adverse health effects, encompassing physical, psychological, social, and neurological consequences.

REFERENCES:

Duch, H., Fisher, E. M., Ensari, I., & Harrington, A. (2013). Screen time use in children under 3 years old: a systematic review of correlates. *The international journal of behavioral nutrition and physical activity*, *10*, 102. https://doi.org/10.1186/1479-5868-10-102

Paudel, S., Jancey, J., Subedi, N., & Leavy, J. (2017). Correlates of mobile screen media use among children aged 0-8: a systematic review. *BMJ open*, *7*(10), e014585. https://doi.org/10.1136/bmjopen-2016-014585

Vaala, S., Ly, A., & Levine, M. H. (2015). Getting a Read on the App Stores: A Market Scan and Analysis of Children's Literacy Apps. Full Report. In *Joan Ganz Cooney Center at Sesame Workshop*. Joan Ganz Cooney Center at Sesame Workshop. 1900 Broadway, New York, NY 10023.

Dumuid D. (2020). Screen time in early childhood. *The Lancet. Child & adolescent health*, *4*(3), 169–170. https://doi.org/10.1016/S2352-4642(20)30005-5

Hutton, J. S., Dudley, J., Horowitz-Kraus, T., DeWitt, T., & Holland, S. K. (2020). Associations Between Screen-Based Media Use and Brain White Matter Integrity in Preschool-Aged Children. *JAMA pediatrics*, *174*(1), e193869. https://doi.org/10.1001/jamapediatrics.2019.3869

Bozzola, E., Spina, G., Ruggiero, M., Memo, L., Agostiniani, R., Bozzola, M., Corsello, G., & Villani, A. (2018). Media devices in pre-school children: the recommendations of the Italian pediatric society. *Italian journal of pediatrics*, *44*(1), 69. https://doi.org/10.1186/s13052-018-0508-7

Domingues-Montanari S. (2017). Clinical and psychological effects of excessive screen time on children. *Journal of paediatrics and child health*, *53*(4), 333–338. https://doi.org/10.1111/jpc.13462

American Academy of Pediatrics (AAP), (2016). [Internet] New recommendations for children's electronics media use. ScienceDaily. 21 October 2016. https://www.sciencedaily.com/releases/2016/10/161021121843.htm .

Lui, D. P., Szeto, G. P., & Jones, A. Y. (2011). The pattern of electronic game use and related bodily discomfort in Hong Kong primary school children. *Computers & Education*, *57*(2), 1665-1674.

Institute for health Metrics and Evaluation–IHME HealthData.org 2015. [(accessed on 1 September 2016)]; Available online: http://vizhub.healthdata.org/gbd-compare/

Fares, J., Fares, M. Y., & Fares, Y. (2017). Musculoskeletal neck pain in children and adolescents: risk factors and complications. *Surgical neurology international*, *8*.

TEXT NECK ®: A Global Epidemic. the text neck Institute. [(accessed on 29 August 2016)]; Available online: http://text-neck.com

Hansraj K. K. (2014). Assessment of stresses in the cervical spine caused by posture and position of the head. *Surgical technology international*, *25*, 277–279.

Toh, S. H., Coenen, P., Howie, E. K., & Straker, L. M. (2017). The associations of mobile touch screen device use with musculoskeletal symptoms and exposures: A systematic review. *PloS one*, *12*(8), e0181220. https://doi.org/10.1371/journal.pone.0181220

Akinbinu, T. R., & Mashalla, Y. J. (2014). Impact of computer technology on health: Computer Vision Syndrome (CVS). *Medical Practice and Reviews*, *5*(3), 20-30.

Varma, R., Deneen, J., Cotter, S., Paz, S. H., Azen, S. P., Tarczy-Hornoch, K., Zhao, P., & Multi-Ethnic Pediatric Eye Disease Study Group (2006). The multi-ethnic pediatric eye disease study:

design and methods. *Ophthalmic epidemiology*, *13*(4), 253–262. https://doi.org/10.1080/09286580600719055

Courage, M. L., & Setliff, A. E. (2010). When babies watch television: Attention-getting, attention-holding, and the implications for learning from video material. *Developmental Review*, *30*(2), 220-238.

Shenouda, N., & Timmons, B. W. (2012). Preschool Focus: Physical Activity and Screen Time. *Hamilton, Ont.: Child Health and Exercise Medicine Program. McMaster University*, (5).

Council on Communications and Media, & Strasburger, V. C. (2011). Children, adolescents, obesity, and the media. *Pediatrics*, *128*(1), 201–208. https://doi.org/10.1542/peds.2011-1066

Biddle, S. J., García Bengoechea, E., & Wiesner, G. (2017). Sedentary behaviour and adiposity in youth: a systematic review of reviews and analysis of causality. *The international journal of behavioral nutrition and physical activity*, *14*(1), 43. https://doi.org/10.1186/s12966-017-0497-8

Goldfield, G. S., Kenny, G. P., Hadjiyannakis, S., Phillips, P., Alberga, A. S., Saunders, T. J., Tremblay, M. S., Malcolm, J., Prud'homme, D., Gougeon, R., & Sigal, R. J. (2011). Video game playing is independently associated with blood pressure and lipids in overweight and obese adolescents. *PloS one*, *6*(11), e26643. https://doi.org/10.1371/journal.pone.0026643

Sharma, S., Merghani, A., & Mont, L. (2015). Exercise and the heart: the good, the bad, and the ugly. *European heart journal*, *36*(23), 1445–1453. https://doi.org/10.1093/eurheartj/ehv090

Curtis, B. M., & O'Keefe, J. H., Jr (2002). Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clinic proceedings*, *77*(1), 45–54. https://doi.org/10.4065/77.1.45

Hsieh, D. L., & Hsiao, T. C. (2016). Respiratory sinus arrhythmia reactivity of internet addiction abusers in negative and positive emotional states using film clips stimulation. *Biomedical engineering online*, *15*(1), 69. https://doi.org/10.1186/s12938-016-0201-2

Straube, A., Heinen, F., Ebinger, F., & von Kries, R. (2013). Headache in school children: prevalence and risk factors. *Deutsches Arzteblatt international*, *110*(48), 811–818. https://doi.org/10.3238/arztebl.2013.0811

Falkenberg, H. K., Johansen, T. R., & Thorud, H. M. S. (2020). Headache, eyestrain, and musculoskeletal symptoms in relation to smartphone and tablet use in healthy adolescents.

Hrafnkelsdottir, S. M., Brychta, R. J., Rognvaldsdottir, V., Gestsdottir, S., Chen, K. Y., Johannsson, E., Guðmundsdottir, S. L., & Arngrimsson, S. A. (2018). Less screen time and more frequent vigorous physical activity is associated with lower risk of reporting negative mental health symptoms among Icelandic adolescents. *PloS one*, *13*(4), e0196286. https://doi.org/10.1371/journal.pone.0196286

Attygalle, U. R., Hewawitharana, G., & Wijesinghe, C. J. (2020). Migraine, attention deficit hyperactivity disorder and screen time in children attending a Sri Lankan tertiary care facility: are they associated?. *BMC neurology*, *20*(1), 275. https://doi.org/10.1186/s12883-020-01855-5

Lund, J., Berring-Uldum, A., Colak, M., & Debes, N. M. M. (2022). Headache in Children and Adolescents: The Association between Screen Time and Headache within a Clinical Headache Population. *Neuropediatrics*, *53*(4), 221–226. https://doi.org/10.1055/s-0041-1740550

Çaksen H. (2021). Electronic Screen Exposure and Headache in Children. *Annals of Indian Academy of Neurology*, *24*(1), 8–10. https://doi.org/10.4103/aian.AIAN_972_20

Bureau, M., Hirsch, E., & Vigevano, F. (2004). Epilepsy and videogames. *Epilepsia*, *45 Suppl 1*, 24–26. https://doi.org/10.1111/j.0013-9580.2004.451003.x

Nikkelen, S. W., Valkenburg, P. M., Huizinga, M., & Bushman, B. J. (2014). Media use and ADHD-related behaviors in children and adolescents: A meta-analysis. *Developmental psychology*, *50*(9), 2228–2241. https://doi.org/10.1037/a0037318

Tamana, S. K., Ezeugwu, V., Chikuma, J., Lefebvre, D. L., Azad, M. B., Moraes, T. J., Subbarao, P., Becker, A. B., Turvey, S. E., Sears, M. R., Dick, B. D., Carson, V., Rasmussen, C., CHILD study Investigators, Pei, J., & Mandhane, P. J. (2019). Screen-time is associated with inattention problems in preschoolers: Results from the CHILD birth cohort study. *PloS one*, *14*(4), e0213995. https://doi.org/10.1371/journal.pone.0213995

Tan, T. X., & Zhou, Y. (2022). Screen Time and ADHD Behaviors in Chinese Children: Findings From Longitudinal and Cross-Sectional Data. *Journal of attention disorders*, *26*(13), 1725–1737. https://doi.org/10.1177/10870547221098181

Biçer, BB. (2020). Evaluation of Screen Exposure and Parental Internet Safety and Conscious Internet Use Knowledge in Children Diagnosed with Attention Deficit and Hyperactivity Disorder Between the Ages of 6-12.

Cheung, C. H., Bedford, R., Saez De Urabain, I. R., Karmiloff-Smith, A., & Smith, T. J. (2017). Daily touchscreen use in infants and toddlers is associated with reduced sleep and delayed sleep onset. *Scientific reports*, *7*, 46104. https://doi.org/10.1038/srep46104

Dong, H. Y., Wang, B., Li, H. H., Yue, X. J., & Jia, F. Y. (2021). Correlation Between Screen Time and Autistic Symptoms as Well as Development Quotients in Children With Autism Spectrum Disorder. *Frontiers in psychiatry*, *12*, 619994. https://doi.org/10.3389/fpsyt.2021.619994

Kushima, M., Kojima, R., Shinohara, R., Horiuchi, S., Otawa, S., Ooka, T., Akiyama, Y., Miyake, K., Yokomichi, H., Yamagata, Z., & Japan Environment and Children's Study Group (2022). Association Between Screen Time Exposure in Children at 1 Year of Age and Autism Spectrum Disorder at 3 Years of Age: The Japan Environment and Children's Study. *JAMA pediatrics*, *176*(4), 384–391. https://doi.org/10.1001/jamapediatrics.2021.5778

Maras, D., Flament, M. F., Murray, M., Buchholz, A., Henderson, K. A., Obeid, N., & Goldfield, G. S. (2015). Screen time is associated with depression and anxiety in Canadian youth. *Preventive medicine*, *73*, 133–138. https://doi.org/10.1016/j.ypmed.2015.01.029

Liu, M., Wu, L., & Yao, S. (2016). Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies. *British journal of sports medicine*, *50*(20), 1252–1258. https://doi.org/10.1136/bjsports-2015-095084

Schou Andreassen, C., Billieux, J., Griffiths, M. D., Kuss, D. J., Demetrovics, Z., Mazzoni, E., & Pallesen, S. (2016). The relationship between addictive use of social media and video games and symptoms of psychiatric disorders: A large-scale cross-sectional study. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*, *30*(2), 252–262. https://doi.org/10.1037/adb0000160

Anderson, C. A., Bushman, B. J., Bartholow, B. D., Cantor, J., Christakis, D., Coyne, S. M., Donnerstein, E., Brockmyer, J. F., Gentile, D. A., Green, C. S., Huesmann, R., Hummer, T., Krahé, B., Strasburger, V. C., Warburton, W., Wilson, B. J., & Ybarra, M. (2017). Screen Violence and Youth Behavior. *Pediatrics*, *140*(Suppl 2), S142–S147. https://doi.org/10.1542/peds.2016-1758T

CHAPTER VI

Eatıng Dısorders

Gülfer AKÇA[1]

Introduction

More than 300 years ago, the earliest medical explanation for an adolescent patient with an eating disorder existed, and in 1888 the first case of anorexia nervosa documented in The Lancet was reported. The case of a fourteen-year-old adolescent girl who was noticeably emaciated and refused to eat for no apparent reason is described in the scientific article (Gull 1888). Bulimia nervosa was described between the 1930s and 1940s as a combination of "reversing food" and self-vomiting, linked to severe weight gain and distorted body image. (Habermas 1989). Today, the pathophysiology and psychobiology of eating disorders remain difficult to fully understand (Weiselberg, Gonzalez & Fisher 2011). Eating disorders are not a simple concern about physical appearance,

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but serious diseases that can reach life-threatening dimensions. They are serious brain-based disorders with significant medical and psychiatric morbidity and mortality (Chew & Temples, 2022). People experience serious deterioration in their body and weight perception and diet. In particular, adolescence is a complex developmental period that covers the transition from childhood to adolescence and leads to many physical, psychological, hormonal and social changes. The increase in the rate of growth and development increases the need for food and energy in this period. As a result, eating disorders in adolescents slow down or even stop healthy growth and development and increase the risk of diet-related diseases (Baceviciene & Jankauskiene 2020).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-5*) is the latest work to define and categorize eating disorders (American Psychiatric Association 2013) and places more emphasis on behavioral criteria rather than cognitive ones, thus clarifying these conditions in children without eating disorders. The DSM-5 diagnostic criteria for many eating disorders common in children and adolescents are presented in table 1.

Prevalance

The prevalence of eating disorders in adolescents varies. This is mainly due to variation in study populations and the criteria used to define eating disorders. (Smink, Van Hoeken, & Hoek 2012) in a systematic review assessing the lifetime prevalence of eating disorders, frequencies ranged from 1.0% to 22.7% for women and 0.3% to 0.6% for men. Lindvall & Wisting 2016), a cross-sectional study involving more than 10,000 U.S. adolescents aged 13-18 found a prevalence rate of 0.3% for Anorexia, 0.9% for Bulimia and 1.6% for Binge eating disorder (Silén & Keski-Rahkonen 2022). In a study that lasted more than a decade, 5.5-17.9% of young women and 0.6-2.4% of young men experienced a DSM-5 eating disorder in early adulthood.

Lifetime DSM-5 anorexia nervosa was determined as 0.1-0.3% of men and 0.8-6.3% of women, bulimia nervosa was

determined as 0.1-0.2% of men and 0.8-2.6% of women, binge eating disorder was determined as 0.3-0.7% of men and 0.6-6.1% of women. Emerging studies in Eastern Europe, Asia, and Latin America show similarly high prevalences (Silen & Keski-Rahkonen 2022)

In industrialized countries, eating disorders are the third most common chronic disease in adolescent girls, after obesity and asthma (Peláez, Encinas &Escursell, 2005). In studies examining the relationship between obesity and eating disorders, it is emphasized that adolescents who were previously diagnosed with obesity later received eating disorder treatment. (Lebow, Sim & Kransdorf 2015) Obesity, which is a medical disease, is not considered as an eating disorder in psychiatric classifications. However, considering its close connection with mental factors and its psychological consequences, obesity is a diagnostic group that deserves psychiatric evaluation (Llewellyn & Wardle 2015). In particular, the binge eating disorder group constitutes a subgroup of obesity.

Etiology

Adolescence is a period in which physical appearance gains importance and feelings about the body change. Due to the negative aspects of body image such as the idea that thinness is ideal, dissatisfaction with one's body, being overweight and ashamed of one's body, irregular eating and eating disorders occur in adolescents. This is the result of relational, biological, and psychological predisposition, family communication, and the interaction of social conditions (Krug et al. 2013). It has also been shown that there is a strong and consistent relationship between social media use and eating anxiety. (Sidani et al. 2016)

It has been determined that the level of anxiety in children increases due to the fact that families make critical statements to their children in terms of weight and attach excessive importance to appearance, body dissatisfaction gradually increases, and behaviors such as frequent dieting and bulimia nervosa develop. (Rodgers & Chabrol 2009) In addition, it has been observed that peer groups

significantly affect the child's body image by discriminating based on pressure or image on diet. (Helfert & Warschburger 2011)

Differential Diagnosis

Differential diagnosis should be made with all kinds of physical diseases that lead to weight loss. Systemic diseases such as malignancy, inflammatory bowel diseases, celiac disease, endocrine and metabolic diseases, and infection should be excluded. Within psychiatric disorders, they are likely to be seen together with mood disorders and anxiety disorders. Tumors of the central nervous system in relation to overeating should be differentially diagnosed with Klein-Levin syndrome. Substance use disorders, mood disorders, anxiety disorders are associated with panic attacks.

Types of eating disorders

Anorexia Nervoza

Anorexia nervosa (AN) is the third most common chronic disease in young people. AN is an eating disorder that leads the patient to various specific behaviors (such as excessive restriction of food intake, self-vomiting, excessive exercise, laxative-diuretic use) in order to lose weight due to the desire to be weak and appreciated and excessive fear of obesity. Due to this condition, the body weight and shape of the individual are usually impaired. (Westmoreland, Krantz & Mehler 2016)

Bulimia Nervoza

Bulimia nervosa (BN) is a condition that encompasses behaviors aimed at controlling body weight. Since the person cannot control the overeating attacks, he willingly uses methods such as vomiting, laxatives, diuretics, enemas and excessive exercise to prevent weight gain afterwards. The frequency with which they engage in these behaviors determines the severity of this disorder. An individual's self-esteem varies in proportion to their body shape and weight. (Westmoreland, Krantz & Mehler 2016)

Binge Eating Disorder (BED)

It is an eating disorder in which the individual consumes a much larger amount of food in a short period of time (for example, every 2 hours) and under the same conditions, in which many people cannot control the eating behavior, and is associated with the presence of repetitive excessive eating behavior. (American Psychiatric Association 2013) The main feature of BED is the effort to remove the calories from the food with specific movements such as forcing the patient to vomit himself, using laxative or diuretic drugs, or accelerating metabolism with excessive exercise after binge eating attacks (Halmi 2003) .

Atypical eating disorders not otherwise specified

This type of disorder is a feeding and eating disorder that causes clinically significant distress or impairment in the individual in social, occupational, or other important areas, but does not meet other nutritional disorder diagnostic criteria. In order to receive the diagnosis of "not otherwise named": Have all the symptoms of AN, except for the weight being within normal values; meet all the criteria of BN except for the absence of binge eating behavior or inappropriate compensatory behaviors/frequency of less than 1 per week within 3 months; Except that the frequency of binge eating behavior is less than 1 per week within 3 months, it should be in a table that does not include other eating disorders, such as meeting all the criteria of TYD. (American Psychiatric Association 2013)

Outflow and Outcome

Complete recovery is reported in approximately half of the patients with AN, moderate recovery in 30%, and poor outcome in 20%. Complete recovery in adolescents with good treatment is up to 70% (Yager et al. 2006) It is reported that recovery rates are better in BN than in AN. It should be remembered that in both diseases, chronic course and the presence of relapses. Early diagnosis and treatment increase recovery rates.

Initial evaluation is very important in patients in terms of clinical course. Initial assessment; Nutrition should include determining the degree of malnutrition, observing acute complications and assessing the psychological state. Diet, hunger, vomiting, use of laxatives/diuretics, excessive consumption of prescription/over-the-counter weight loss drugs, excessive exercise should be examined, abnormal eating behaviors and weight changes (weight loss-gain, periodic fluctuations), lengthening, and age-appropriateness of sexual development should be checked (Golden et al. 2015). Especially in determining the degree of malnutrition, body mass index (BMI), body weight (kg)/height (m^2) should be calculated by measuring weight and height and evaluation should be made according to growth curves. The degree of malnutrition should be calculated by calculating BMI, Z score and percentage of weight loss. A suggested adaptation of existing classifications for use in adolescents and young adults with eating disorders is shown in table 2. (Golden et al. 2015)

In cases where there is no response to outpatient treatment, hospitalization criteria should be evaluated. These criteria are given in Table 2. Early recognition and intervention of eating disorders is important. Diagnostic criteria and approach to eating disorders in primary care institutions should be well known and due attention should be paid to the issue (Chew & Temples 2022). Multidisciplinary teamwork is required for effective treatment. This team should include physicians, psychiatrists, dieticians, nurses, and these experts, who are experts in their fields, should evaluate the physical characteristics, emotional state, family and school problems of the adolescent together. If there is neglect/abuse of the child, the social counselor may request special support and the use of legal powers when necessary (Golden et al. 2015). A basic treatment approach has not yet been adopted. Different psychotherapy methods, family therapy, medication and, if necessary, hospital treatment should be put into use taking into account the patient's unique situation. The goal of treatment should be to achieve a normal, healthy, individualized, stable body weight, to control

abnormal eating behaviors, and to prevent recurrence. Within this framework, medical interventions related to nutrition and correction of somatic condition should also be included

Result

Eating disorders are a group of psychiatric disorders with biological, psychological and sociocultural dimensions. The fact that it affects young people in particular and the increasing size of this effect is closely related to physicians, educators and parents working in every branch. Since their treatment is difficult, long and expensive, the importance of protective and preventive efforts in social and educational terms cannot be discussed. Since early diagnosis and guidance are vital, our colleagues have an important responsibility in this regard.

Table 1. Diagnostic Features of Eating Disorders Commonly Seen in Children and Adolescents

DSM-5 Eating Disorder Diagnosis	**Diagnostic Features**
Anorexia nervosa (AN)	A. Restricted caloric intake relative to energy requirements, leading to significantly low body weight for age, sex, projected growth, and physical health
	B. Intense fear of gaining weight or behaviors that consistently interfere with weight gain, despite being at a significantly low weight
	C. Altered perception of one's body weight or shape, excessive influence of body weight or shape on self-value, or persistent lack of acknowledgment of the seriousness of one's low body weight
	Subtypes: restricting type (weight loss is achieved primarily through dieting, fasting, and/or excessive exercise. In the previous 3 mo, there have been no repeated episodes of binge eating or purging); binge-eating/purging type (in the previous 3 mo, there have been repeated episodes of binge eating or purging; ie, self-induced vomiting or misuse of laxatives, diuretics, or enemas)

Bulimia nervosa (BN)	Repeated episodes of binge eating. Binge eating is characterized by both of the following: within a distinct period of time (eg, 2 h), eating an amount of food that is clearly larger than what most individuals would eat during a similar period of time under similar circumstances and a sense that one cannot limit or control their overeating during the episode
	The binge-eating episodes include 3 or more of the following: eating much more quickly than normal, eating until uncomfortably full, eating large amounts of food when not feeling hungry, eating alone because of embarrassment at how much one is eating, and feeling guilty, disgusted, or depressed afterward
	Marked anguish is experienced regarding binge eating
	On average, the binge eating occurs at least once a week for 3 mo
	The binge eating is not associated with the use of inappropriate compensatory behavior as in BN and does not occur only in the context of BN or AN
Avoidant/restrictive food intake disorder (ARFID)	A disrupted eating pattern (eg, seeming lack of interest in eating or food; avoidance based on the sensory qualities of food; concern about unpleasant consequences of eating) as evidenced by persistent failure to meet appropriate nutritional and/or energy needs associated with 1 (or more) of the following: significant weight loss or, in children, failure to achieve expected growth and/or weight gain, marked nutritional deficiency, reliance on enteral feeding or oral nutritional supplements, significant interference with psychosocial functioning
	The disturbance cannot be better explained by lack of available food or by an associated culturally sanctioned practice

	The eating disturbance cannot be attributed to a coexisting medical condition nor better explained by another mental disorder. If the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder
Other specified feeding or eating disorders, examples	Atypical AN: all of the criteria for AN are met yet the individual's weight is within or above the normal range despite significant weight loss
	BN (of low frequency and/or limited duration): All of the criteria for BN are met, but, on average, the binge eating and compensatory behaviors occur less than once a week and/or for <3 mo
	BED (of low frequency and/or limited duration): All of the criteria for BED are met, but, on average, the binge eating occurs less than once a week and/or for <3 mo
	Purging disorder: recurrent purging behavior (eg, self-induced vomiting; misuse of laxatives, diuretics, or other medications) in the absence of binge eating with the intent to influence weight or body shape

Table 2. A proposed classification of the degree of malnutrition for adolescents with eating disorders

	Mild	Moderate	Severe
% median BMI	80%–90%	70%–79%	<70%
BMI z score	−1 to −1.9	−2 to −2.9	−3 or greater
Weight loss	>10% body mass loss	>15% body mass loss	>20% body mass loss in 1 year or >10% body mass loss in 6 months

BMI = body mass index

Table 3. Criteria for hospitalization in eating disorders

- Expected body weight of 75% or less based on age and gender
- Dehydration
- Electrolyte imbalances (hypokalemia, hyponatraemia and hypopotasemia)
- Cardiac disorders (severe bradycardia, prolonged QT interval)
- Deterioration in physiological parameters
    - Severe bradycardia (daytime CTA≤50/min; nighttime CTA≤45/min)
    - Hypothermia (body temperature≤35.6 °C)
    - Lag in growth and development
- Patients who do not get results in outpatient treatment
- Refusal to eat, uncontrollable eating behavior and vomiting
- Need for medical treatment due to malnutrition

- Presence of significant depression or other major psychiatric problems requiring inpatient treatment

References

Gull W. (1888); Anorexia nervosa. *Lancet.* 131:516–517. doi: 10.1016/S0140-6736(00)48519-3

Habermas T.(1989) The psychiatric history of anorexia nervosa and bulimia nervosa: Weight concerns and bulimic symptoms in early case reports. *Int. J. Eat. Disord*; 8:259–273. doi: 10.1002/1098-108X(198905)8:3<259:AID-EAT2260080302>3.0.CO; 2-#

Weiselberg EC, Gonzalez M, Fisher M. (2011) Eating disorders in the twenty-first century. *Minerva Ginecologica*. Dec; 63(6):531-545. PMID: 22036757

Chew KK, Temples HS. (2022) Adolescent Eating Disorders: Early Identification and Management in Primary Care. *J Pediatr Health Care*. Nov-Dec; 36(6):618-627. doi: 10.1016/j.pedhc.2022.06.004. Epub 2022 Oct 28. PMID: 37855407.

Baceviciene M, Jankauskiene R. (2020) Associations between Body Appreciation and Disordered Eating in a Large Sample of Adolescents. *Nutrients.* 2020 Mar 12; 12(3):752. doi: 10.3390/nu12030752. PMID: 32178334; PMCID: PMC7146197.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders 5th ed. Washington, DC American Psychiatric Association Publishing Arlington: American Psychiatric Association: 329-354.

Smink FRE, Van Hoeken D, Hoek HW (2012) Epidemiology of eating disorders: incidence, prevalence and mortality rates *Curr Psychiatry Rep* 2012 14(4):406–414 doi 10.1007/s11920-012-0282-y

Lindvall Dahlgren C, Wisting L. (2016); Transitioning from DSM-IV to DSM-5: A systematic review of eating disorder prevalence assessment. *Int J Eat Disord*; 49(11): 975-997 doi:10.1002/eat.22596

Silén Y, Keski-Rahkonen A.(2022) Worldwide prevalence of DSM-5 eating disorders among young people. Curr Opin Psychiatry. Nov 1; 35(6):362-371. doi: 10.1097/YCO.0000000000000818. Epub 2022 Sep 13. PMID: 36125216

Peláez Fernández, M.Á.; Labrador Encinas, F.J.; Raich Escursell, R.M (2005). Prevalence of Eating Disorders: Methodological Considerations. *International Journal of Psychology and Psychological Therapy*, vol. 5, no. 2, july, pp. 135-148 Almeria, Spain

Krug, I., Villarejo, C., Jiménez-Murcia, S., Perpina, C., Vilarrasa, N., Granero, R., et al. (2013). Eating-related environmental factors in underweight eating disorders and obesity: are there common vulnerabilities during childhood and early adolescence?. *European Eating Disorders Rev*iew, 21(3):202-08 doi : 10.1002/erv.2204

Lebow, J., Sim, L.A., Kransdorf, L.N. (2015). Prevalence of a history of overweight and obesity in adolescents with restrictive eating disorders. *Journal of Adolescent Health,* 56(1):19-24 doi:10.1016/j.jadohealth.2014.06.005

Llewellyn, C, Wardle, J .(2015) Behavioral susceptibility to obesity: gene-environment interplay in the development of weight. *Physiol Behav* 152(PtB): 494–501 doi.org/10.1016/j.physbeh.2015.07.006

Sidani JE, Shensa A, Hoffman B, Hanmer J, Primack BA. (2016) The Association between Social Media Use and Eating Concerns among US Young Adults. *J Acad Nutr Diet.* Sep; 116(9):1465-1472. doi: 10.1016/j.jand.2016.03.021. Epub 2016 May 5. PMID: 27161027; PMCID: PMC5003636.,

Rodgers R., Chabrol, H. (2009) Parental attitudes, body image disturbance and disordered eating amongst adolescents and young adults: A review. *European Eating Disorders Review,* 17(2):137-51. DOİ: 10.1002/erv.907

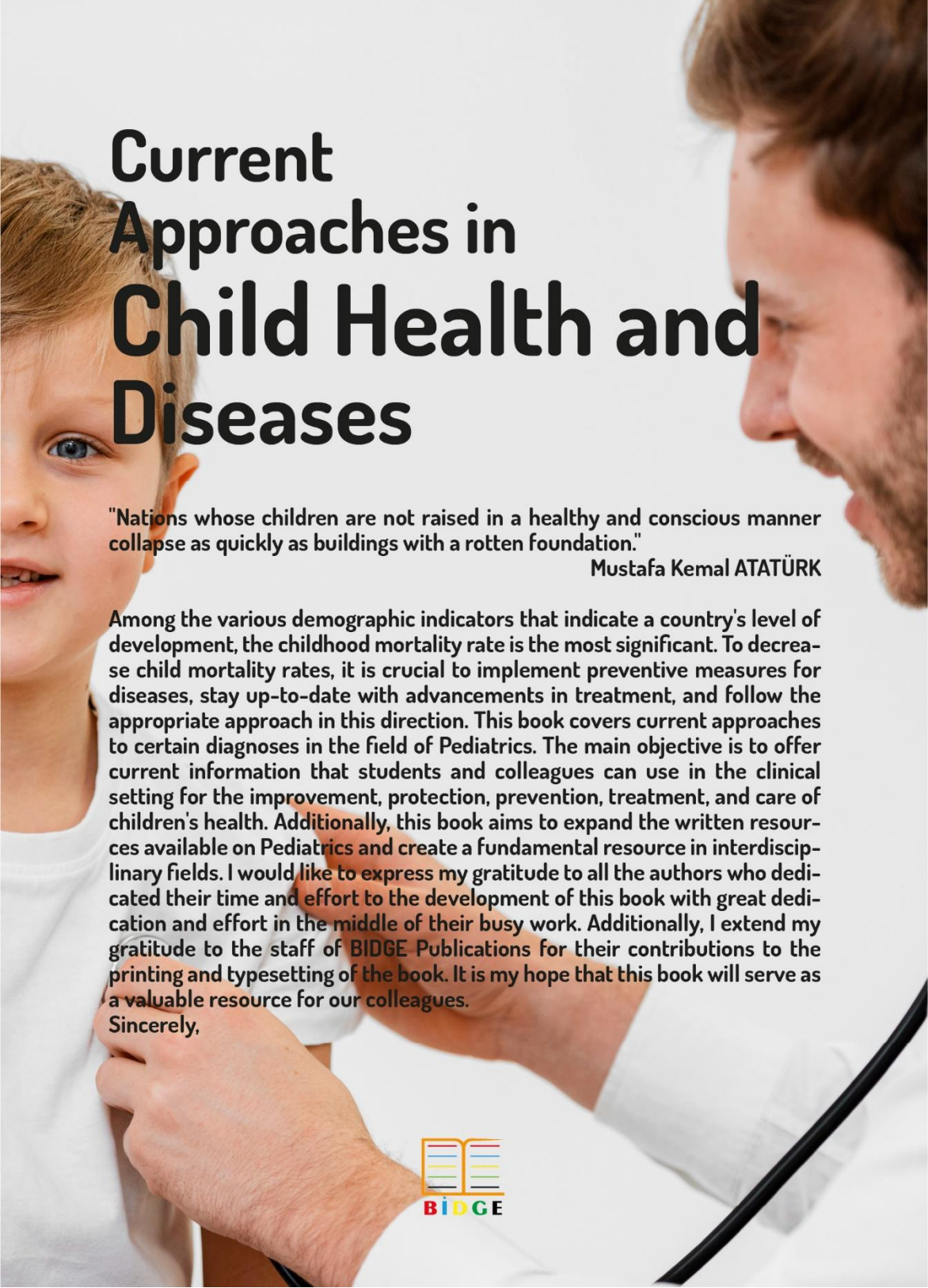
Helfert, S., Warschburger, P. (2011) A prospective study on the impact of peer and parental pressure on body dissatisfaction in adolescent girls and boys. *Body Image*, 8(2):101-9 doi: 10.1016/j.bodyim.2011.01.004

Yager J, Devlin MJ, Halmi KA, et al. (2006) Practice guideline for the treatment of patients with eating disorders, 3rd ed. Washington: *American Psychiatric Association*; 29-33.

Golden, N.H., Katzman, D.K., Sawyer, S.M., Ornstein, R.M., Rome, E.S., Garber, A.K., et al. (2015). Update on the medical management of eating disorders in adolescents. *Journal of Adolescent Health*, 56(4):370-75. Doi:10.1016/j.jadohealth.2014.11.020

Westmoreland P, Krantz MJ, Mehler PS. (2016) Medical Complications of Anorexia Nervosa and Bulimia. *Am J Med*. 2016 Jan; 129(1):30-7. doi: 10.1016/j.amjmed.2015.06.031. Epub 2015 Jul 10. PMID: 26169883.

Halmi KA. (2003) Classification, diagnosis and comorbidities of eating disorders: a review. *Eating Disorders.* WPA Series. West Sussex: John Wiley & Sons 1-33. doi:10.1002/0470867183.ch1



Current Approaches in Child Health and Diseases

"Nations whose children are not raised in a healthy and conscious manner collapse as quickly as buildings with a rotten foundation."

Mustafa Kemal ATATÜRK

Among the various demographic indicators that indicate a country's level of development, the childhood mortality rate is the most significant. To decrease child mortality rates, it is crucial to implement preventive measures for diseases, stay up-to-date with advancements in treatment, and follow the appropriate approach in this direction. This book covers current approaches to certain diagnoses in the field of Pediatrics. The main objective is to offer current information that students and colleagues can use in the clinical setting for the improvement, protection, prevention, treatment, and care of children's health. Additionally, this book aims to expand the written resources available on Pediatrics and create a fundamental resource in interdisciplinary fields. I would like to express my gratitude to all the authors who dedicated their time and effort to the development of this book with great dedication and effort in the middle of their busy work. Additionally, I extend my gratitude to the staff of BIDGE Publications for their contributions to the printing and typesetting of the book. It is my hope that this book will serve as a valuable resource for our colleagues.

Sincerely,

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