Neuroendocrinology Letters Volume 44 No. 7 2023
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

REVIEW ARTICLE

Early oral hydration in patients with high enterocutaneous fistula

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Submitted: 2023-07-07 *Accepted: 2023-08-27* *Published online: 2023-09-24*

Key words: **enterocutaneous fistula; oral rehydration salt solution; hypotonic fluids; tea; sodium-dependent glucose cotransporters**

Neuroendocrinol Lett 2023; **44**(7):432–438 **PMID:** 37874556 NEL440723R01 © 2023 Neuroendocrinology Letters • **www.nel.edu**

Abstract

INTRODUCTION: Enterocutaneous fistula is defined as an abnormal connection between the gastrointestinal tract and the skin. In addition to the early recognition and treatment of sepsis, nutritional support, wound management, the adequate replacement of lost fluids with a properly set and timely rehydration treatment, together with the control of fistula production represent the first steps in treatment management.
MATERIAL AND METHODS: The authors present an overview of oral rehydration therapy, describing the properties and effects of individual solutions on fistula. The absorption of fluids and electrolytes into the gastrointestinal tract is performed by the group of sodium-dependent glucose cotransporters (sodium-glucose linked transporter, SGLT1).
DISCUSSION: The water and electrolyte absorption mechanisms described in the article can be used in the treatment of a patient with a high fistula. The amount of administered hypotonic fluids (water, tea) should not exceed 500 ml/day. The remaining volume, depending on fistula loss, must be supplemented with isoosmolar fluids. With a good tolerance of oral rehydration solutions and compliance with the other steps of treatment, it is possible to remain on oral intake during the entire duration of treatment without the need to prohibit it completely, thus improving the patient's overall comfort.
CONCLUSION: Reducing the intake of hypotonic fluids (tap water, tea) and administering an isotonic solution help to reduce the production of the fistula, thereby contributing to its spontaneous closure.

INTRODUCTION

We define a fistula as an abnormal connection between two epithelialized surfaces. Most often, it is a communication between one organ and another organ, skin or wound. The connection between one part of the intestinal tract and another part of the body is generally called a gastrointestinal fistula (GIF) (Tong *et al.* 2012).

An enterocutaneous fistula (ECF) is an abnormal tube-shaped communication that connects the gastrointestinal tract to the external environment on the surface of the skin. A subtype of ECF is the enteroatmospheric (EAF) fistula, where the main difference is the absence of tissue overlying the fistula and the communication between the external environment and the gastrointestinal tract is direct (Ghimire 2022).

Enterocutaneous fistulas (ECF) are associated with significant morbidity and mortality and cause significant patient distress (Haack *et al.* 2014). The prognosis of a patient with a fistula depends mainly on the general condition of the patient, their nutritional status, comorbidities and the nature of the fistula. The main goal is to achieve closure of the fistula, either spontaneously or with the help of surgery. Among the main factors that cause a delay in the spontaneous closure of the fistula are old age, malnutrition, a fistula with high production (over 500 ml/day), the presence of a fistula lasting over 5 weeks, malignant etiology, an anatomical location in the upper part of the gastrointestinal tract or incorrect treatment management (Cozzaglio *et al.* 2007).

Sepsis, malnutrition, and electrolyte abnormalities represent the typical triad of complications in patients with this problem. The management of ECF treatment is a complex multidisciplinary process. The initial focus of therapy should be treating fluid disorders, controlling fistula production, correcting the electrolyte balance, and aggressively treating septic manifestations (Tang *et al.* 2020).

The importance of timely oral rehydration treatment is confirmed by the fact that many patients with ECF are depleted of salt and water internally. The proof behind this statement is the result of observations where high plasma levels of renin and aldosterone were recorded in patients with ECF, indicating a strong compensatory mechanism of the organism. Unrecognized dehydration due to ECF poses a significant risk to patients with advanced renal insufficiency, in which case it may lead to renal failure. Abnormalities in the mineralogram can also cause various cardiac arrhythmias (Kennedy *et al.* 1983).

The aim of this article is to present a contemporary view on the issue of oral fluid replacement, to compare the properties and to describe the effect of individual oral solutions that can be used as part of rehydration treatment.

PHYSIOLOGICAL SECRETION OF THE GASTROINTESTINAL TRACT

The intestinal mucosa is a semipermeable membrane that separates the intestinal lumen from the vascular bed, while also allowing the two-way passage of several substances. Secretion and absorption are the two basic functions of the epithelial cells of the small intestine (Ghishan *et al.* 2012). In a healthy individual, the daily production of secretions in the gastrointestinal tract reaches an average of approximately 4 litres. This consists of 0.5 l of saliva, 2 l of gastric acid and 1.5 of pancreaticobiliary secretion, which are produced in response to the food and drink consumed. In most individuals, around 6-8 litres of chyme passes through the duodenojejunal flexure per day. Out of this amount, up to 98% of the volume is reabsorbed liquid, and only approximately 100-200 ml is excreted in the stool (Arebi *et al.* 2004). To fulfil this task, there are several transport molecules in the small intestine, which interact with each other by a synergistic, additive or antagonistic mechanism. (Ghishan *et al.* 2012).

Due to the pathological communication between the intestine and the skin, the space in which adequate reabsorption can occur is shortened and fluid and mineral losses occur. The loss of 1 litre of extracellular fluid through the fistula represents a loss of approximately 100 mmol Na (range 80-140 mmol/l). It follows that as part of rehydration therapy, it is necessary to replace these mineral losses (Pande *et al.* 2020).

Due to the loss of fluids through the ECF and the leakage of fluids into a third space, deep dehydration, hypovolemia and mineral imbalance occur in the body. The adequate replacement of lost fluids with a properly defined and timely rehydration treatment and control of fistula production are the first step in treatment management (Fischer 1983).

CLASSIFICATION OF FISTULAS

There are several ECF classifications. In addition to anatomical and etiological classifications, the division of fistulas according to the amount of daily production is of practical importance:

- fistula with a high output > 500 ml / 24 hours
- fistula with an average output of 200-500 ml / 24 hours
- fistula with a low output < 200 ml / 24 hours

Fistulas with a low daily output have a better prognosis and a higher probability of spontaneous closure than fistulas with a high output. In some patients, spontaneous closure can occur only with the help of appropriate nutritional support and wound care without the need for surgical intervention (Cozzaglio *et al.* 2010).

Knowing the anatomical location is important from the point of view of prognosis. Fistulas located on the small intestine, so-called high enterocutaneous fistulas (duodenum, jejunum, ileum) are characterized by a secretion that is aggressive towards the skin and surrounding tissues due to the presence of highly concentrated digestive juices. Since most of the absorption takes place in the small intestine, high ECFs generally tend to be high production. Fistulas located on the large intestine, so-called low enterocutaneous fistulas, do not drain the secretion from the small intestine, but rather from the stool, which no longer contains digestive enzymes. Because of this, their aggressiveness is significantly lower, and they have a higher tendency to spontaneously close (Ghimire 2022). Also, the problem with maintaining fluid homeostasis and high production is less common with distal fistulas, as most fluids can be absorbed into the intestine orally above the fistula, provided it is in a functionally intact state (Feldman *et al.* 1991).

According to the organ of origin, ECF can be divided into four categories of fistulas. The first category includes oesophageal and gastroduodenal fistula. The second category includes fistulas originating from the small intestine. The third category includes fistulas from the large intestine, and the last category includes enteroatmospheric fistulas, regardless of the place of their initial localization (Williams *et al.* 2010).

As a result of the abnormal communication caused by the fistula, intestinal contents leave the intestinal lumen, and this can lead to the development of a localized abscess, soft tissue infection, generalized peritonitis or sepsis depending on whether the intestinal fistula communicates with the abdominal cavity or soft tissues. Sepsis combined with malnutrition is the main cause of death in patients with enterocutaneous fistula (Singh *et al.* 2009).

The body attempts to deal with the disturbed continuity of the intestinal tract. Therefore, the gastrointestinal tract goes through three typical phases of adaptation:

- Hypersecretory phase: an initial phase that occurs within three days of fistula formation and may last for one to two months. High fistula production with large volume losses is typical.
- Adaptation phase: follows as a reaction to high volume losses. It starts 5 to 7 days after the fistula is formed and can last up to 12 months. It is characterized by a decrease in production. The speed of adaptation depends on the age of the patient, their general condition, the severity of the underlying disease and the location of the fistula.
- Stabilization phase: the last phase is the completion of adaptation. It is characterized by a further decrease in fistula production and stabilization of the internal environment. This process can take up to 24 months (Williams *et al.* 2010; Adaba *et al.* 2017).

ABSORPTION OF FLUIDS AND ELECTROLYTES IN THE GASTROINTESTINAL TRACT

The small intestine is in a constant dynamic state of secretion and absorption, which in a physiological state causes overall net absorption. In some pathological processes, such as infectious diseases (rotaviruses, cholera), ostomies, fistulas, this balance can be inversely proportional to the predominance of secretion. Secretion is mainly caused by the extrusion of chlorides and bicarbonates through the apical chloride channels after activation by the second messengers cAMP, cGMP and calcium (Lehmann *et al.* 2016).

Absorption of water through the intestinal epithelium is a passive process that depends on the movement of dissolved ions, especially the sodium cation. Sodium absorption occurs through three different mechanisms. Passively moving through the intercellular mucosal cell junctions, actively due to the Na^+/H^+ exchange system on the apical membrane of the enterocyte, which works alone or in conjunction with the Cl^- /HCO^- exchange pump, or as cotransport together with the absorption of nutrients such as glucose and amino acids (Banks *et al.* 2002, Shrimanker *et al.* 2023).

The transport of Na^+ and glucose is made possible by the group of sodium-glucose linked transporters (SGLT1). The transporter for glucose (SGLT1) is in an active state only if the sodium ion Na^+ is also bound and transported at the same time. Sodium ions enter the enterocyte in the direction of the concentration gradient, which is maintained by the Na^+/K^+ pump on the basolateral side of the enterocyte, and glucose is transported against the concentration gradient on the apical side of the membrane. When one glucose molecule is transported, two Na^+ molecules are transported. After entering the enterocyte, sodium, glucose, and amino acids create an osmotic gradient that causes the absorption of water from the lumen (Fig. 1). Transport mediated by SGLT1 enables the absorption of water even in pathological conditions that cause increased secretion in the intestine, because it remains functional. Therefore, this mechanism can also be used in the oral rehydration treatment of ECF (Lehmann *et al.* 2016).

Hypotonic drinks (water, tea, coffee)

Tea and water are the most available and cheapest liquids in the hospital environment. Their use is very wide, but they are often incorrectly indicated. From the point of view of composition and concentration of solutes, tea is a hypoosmolar solution. The osmotically active substances in tea are water and sugar. The presence of the main mineral responsible for water transport – Na^+ is absent here. The osmotically active substance here is only glucose; osmolality reaches a level of around 40-60 mmol/L. Due to the absence of sodium, it is not possible to use the facilitated transport of glucose with sodium. The risk lies in the combination of a sweet taste and a strong feeling of thirst stemming from dehydration, encouraging the patient to drink more. This creates a vicious circle. Sodium and glucose are absent in tap water, and its molality is at a low level of 0-30 mmol/l (Parrish *et al.* 2017).

The response of the intestine to the supply of liquids with a sodium concentration lower than 60 mmol/l is the secretion of sodium into the lumen of the intestine to balance the concentration gradients, while water is transferred, which follows the sodium (Weledji 2017).

Taking hyperosmolar fluids, such as fruit juices, sweetened drinks and sodas, is also considered incorrect. A high concentration of solutes indicates the secretion of water in the enterocytes to dilute the luminal

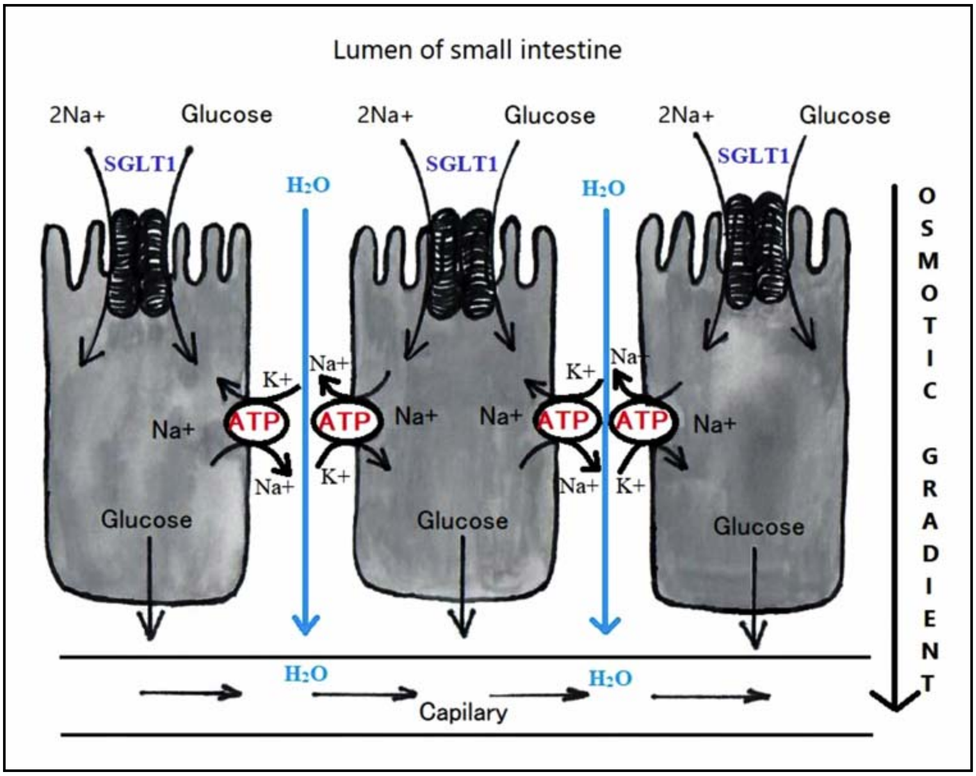

Fig. 1. Transport of water via sodium-glucose linked transporter (SGLT)

content. This leads to further unnecessary fluid losses. It is necessary to realize that, in a physiological state, these fluids could subsequently be absorbed in the ileum and large intestine, but due to the presence of the intestinal fistula, this possibility is impaired (Medlin 2012).

World Health Organization (WHO) oral rehydration salts solution

Oral rehydration salts solution (ORS) is a balanced mixture of glucose and electrolytes, which stimulates fluid absorption in the intestine and thus counteracts dehydration. Originally, this solution was proposed by the World Health Organization and UNICEF and was used in the treatment of dehydration during diarrheal diseases (Buccigrossi *et al.* 2020).

Standard ORS contains NA^+, K^+, Cl^-, citrate and glucose in appropriate amounts (Table 1). This solution occasionally caused hypernatremia, especially in paediatric patients, therefore the concentration of sodium and glucose was reduced, and we use the so-called reduced form.

To achieve the proabsorptive function in the enterocyte, ORS uses Na^+/glucose cotransport via the protein transporter SGLT1. The glucose cotransporter behaves like a water channel. During each transport cycle, two molecules of Na^+ together with one molecule of glucose and hundreds of water molecules are transported into the epithelial cells through SGLT1. The water that is thus transported is hypertonic, resulting in an additional force for transport due to simple osmosis (Loo *et al.* 2002).

When the patient uses a rehydration solution that contains 90 mmol/L of sodium and glucose, it changes the situation in the intestine so that it is not necessary for sodium to be drawn into the lumen, which automatically enables absorption by passive transport. It is proven that such a mechanism, together with the facilitated transport of glucose and sodium, can increase the absorption of water and sodium in the ileum by 20 to 30%. In the jejunum, this effect is even stronger, with fluid absorption up to 60% higher and sodium absorption up to 40% higher (Kelly *et al.* 2004).

Patients can also prepare the rehydration solution at home by simply using measuring cups. It is necessary to mix 20 g of glucose, 2.5 g of sodium bicarbonate and 3.5 g of sodium chloride in 1000 ml of tap water (Medlin 2012).

Tab. 1. Composition of WHO oral rehydration solution (ORS)

	Reduced WHO - ORS	Standard WHO - ORS
Sodium (Na^+) mmmol/l	74	90
Potassium (K^+) mmol/l	20	20
Chlorine (Cl^-) mmol/l	65	80
Citrate µmol/l	520,5	520,5
Glucose, mmmol/l	0,75	1,11
Osmolality, mmol/kg	245	311

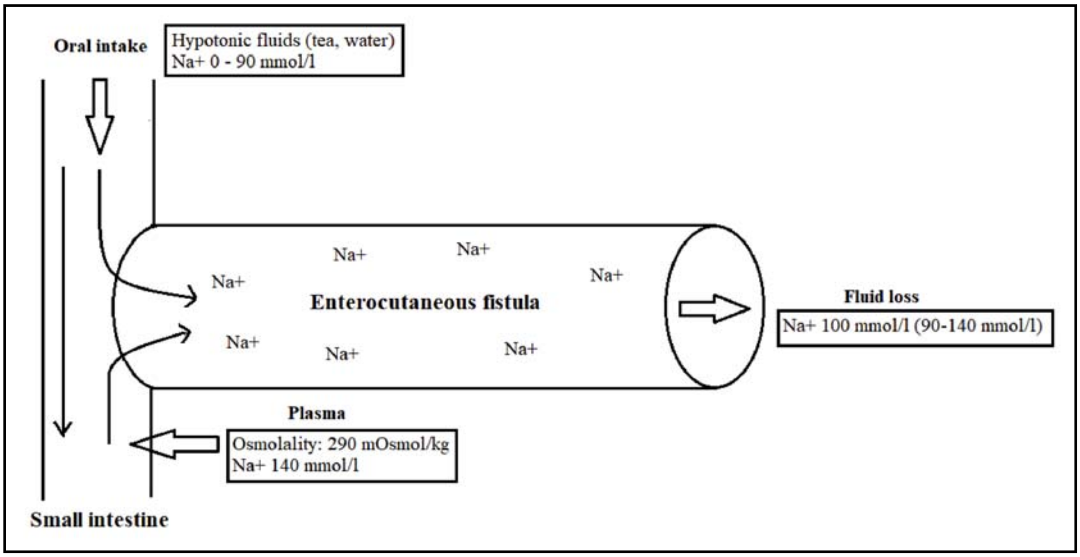

Fig. 2. Demonstration of sodium cation movement in the intestine during intake of a hypotonic solution

DISCUSSION

An overview of retrospective studies shows that most fistulas (75–85%) arise iatrogenically as a complication of abdominal procedures, most often due to a leak or dehiscence anastomoses. The remaining part (15–25%) arises spontaneously. The most common cause of spontaneous fistulas are inflammatory bowel disease, especially IBD (Crohn's disease, ulcerative colitis), appendicitis, diverticulitis, malignant processes, tuberculosis or because of radiation treatment and ischemia (Papa *et al.* 2020; Wright *et al.* 2020).

The water and electrolyte absorption mechanisms described above can be used in the treatment of a patient with a high fistula. With fistulas with high production, the need for fluids can be higher than 5 litres per day. Early oral rehydration treatment aims to prevent the consequences of dehydration and reduce fistula production. A paradox in the management of a patient with an enterocutaneous fistula is the need to limit the intake of certain types of fluids and not let the patient take unlimited amounts of tea and water, which would result in increasing dehydration (Weledji 2017).

The amount of hypotonic fluids (water, tea) administered with ECF should not exceed 500 ml/day. The remaining volume, depending on fistula loss, must be supplemented with isoosmolar fluids (300 mOsm/l) with the target concentration of Na^{+} in the range of 90-120 mmol/l (Arebi *et al.* 2004).

The problem arises if patients with ECF do not follow this regimen and receive fluids that are hypotonic from the point of view of solute concentration, e.g., tea or pure water, where sodium is absent. In liquids with a sodium concentration lower than 90 mmol/L, sodium and water are secreted from the plasma into the lumen intestine, until there is an equalization of concentrations between individual compartments at the level of approximately 100 mmol/L. Subsequently, this fluid is lost along with minerals and other components through the fistula (Fig. 2). With an intact gastrointestinal tract, this extra fluid can be reabsorbed in the ileum or colon (Weledji 2017). This leads to the potentiation of fistula output, which worsens dehydration and malnutrition. Patients are hyponatremic and feel weak, dizzy, or very thirsty. In up to 13% of patients, the concentration of sodium in the urine is below the level of 10 mmol/L. These symptoms, combined with the sweet taste of tea, its practically unlimited availability, can encourage the patient to take more and more hypotonic fluids, leading to a further worsening of the situation. Therefore, we can never recommend patients to drink an unlimited amount of tea, or water (Feldman *et al.* 1991).

Patients with a fistula which has a borderline high output of up to 1,200 ml per day usually manage to maintain a balanced sodium balance by adding extra table salt to food, often to the point of palatability. With losses above 1,200 ml per day, the patient should take ORS to maintain the sodium balance (Nightingale *et al.* 1992).

When using ORS due to the high concentration of sodium and the presence of glucose, water is absorbed in the intestine via SGLT1. This leads to a reduced daily output of the fistula. At the same time, the risk of developing dehydration and electrolyte imbalance is significantly reduced. The patient should be encouraged to take up to two litres of ORS in one day. It is recommended to take small sips at frequent intervals. This solution has a typical taste, which patients describe as drinking "sweet sea water". This can be an obstacle to the patient's compliance; therefore, it is extremely important to explain to the patient the meaning of such a procedure and thus motivate them to cooperate in the treatment process. To reduce the unpleasant taste, it can be taken chilled or flavoured with various fruit flavours (Nightingale 2021).

For proper rehydration treatment, it is essential to monitor the fluid balance. In most cases, fistula production is assessed at 4-to-8-hour intervals until the patient is stabilized. The amount of waste produced and the level of electrolytes in the serum and urine determine the need for treatment (Denicu *et al.* 2022). Another method can be to monitor the concentration of electrolytes in the fluid produced by the fistula, with subsequent adaptation of the composition of the rehydration solution, as close as possible to the produced fluid (Gribovskaja-Rupp *et al.* 2016). Assessing fluid balance and monitoring balance in intake and output helps us prevent the development of multiorgan failure due to significant fluid and electrolyte losses (Denicu *et al.* 2022).

The relationship between a reduction in the volume produced by the fistula and a faster spontaneous closure has not yet been clearly demonstrated, but a reduced production clearly facilitates the maintenance of adequate vascular volume, a stable mineralogram and nutritional status. At the same time, it facilitates fistula care and has a beneficial effect on the skin around the fistula (Galie *et al.* 2006).

A combination of oral rehydration salts solution with sodium-deficient fluid restriction should be sufficient for patients with at least 100 cm of intact intestine remaining above the fistula. If this is not the case, patients usually cannot be managed with an oral regimen alone and they also need parenteral support. With good tolerance of ORS and compliance with the other steps of treatment, it is possible to remain on oral intake during the entire duration of treatment without the need for its complete prohibition, which improves the overall comfort of the patient (Nightingale 2021).

CONCLUSION

ECF fistulas, especially those that are classified as high-volume according to production, are a threat to the patient from the point of view of the development of sepsis, malnutrition, imbalance of water and mineral metabolism. In the treatment regimen, it is essential to follow a multidisciplinary approach. Management includes treating the underlying cause, eliminating the development of sepsis, providing adequate nutrition, and reducing fluid loss (Pande *et al.* 2020). Reducing the intake of hypotonic fluids (tap water, tea) and administering WHO oral rehydration salts solution helps to reduce the production of the fistula, thereby contributing to its spontaneous closure. Thanks to the correct ratio of the minerals contained in ORS, it prevents an increase in dehydration and by replacing minerals that are lost through the fistula, it contributes to the stabilization of the internal environment. The use of ORS in oral fluid supplementation in patients with ECF should be a standard part of the treatment regimen (Metcalf 2019).

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1 Adaba F, Vaizey CJ, Warusavitarne J. Management of Intestinal Failure: The High-Output Enterostomy and Enterocutaneous Fistula. Clin Colon Rectal Surg. 2017 Jul; **30**(3): 215–222. doi: 10.1055/s-0037-1598163. Epub 2017 May 22. PMID: 28684940; PMCID: PMC5498185.

2 Arebi N, Forbes A. High-output fistula. Clin Colon Rectal Surg. 2004 May; **17**(2): 89–98. doi: 10.1055/s-2004-828655. PMID: 20011253; PMCID: PMC2780049.

3 Banks MR, Farthing MJ. Fluid and electrolyte transport in the small intestine. Curr Opin Gastroenterol. 2002 Mar; **18**(2): 176–81. doi: 10.1097/00001574-200203000-00004. PMID: 17033283.

4 Buccigrossi V, Lo Vecchio A, Bruzzese E, Russo C, Marano A, Terranova S, Cioffi V, Guarino A. Potency of Oral Rehydration Solution in Inducing Fluid Absorption is Related to Glucose Concentration. Sci Rep. 2020 May 8; **10**(1): 7803. doi: 10.1038/s41598-020-64818-3. PMID: 32385331; PMCID: PMC7210290.

5 Cozzaglio L, Farinella E, Bagnoli P, Sciannameo F, Doci R. Gastrointestinal fistulas. Nutr Ther Metabol. 2007; **25**: 113–34.

6 Cozzaglio L, Farinella E, Coladonato M, Sciannameo F, Gennari L, Doci R. Current role of surgery in the treatment of digestive fistulas. Ann Ital Chir. 2010 Jul-Aug; **81**(4): 285–94. PMID: 21319701.

7 Denicu MM, Cartu D, Ciorbagiu M, Nemes RN, Surlin V, Ramboiu S, Chiuțu LC. Therapeutic Options in Postoperative Enterocutaneous Fistula-A Retrospective Case Series. Medicina (Kaunas). 2022 Jun 30; **58**(7): 880. doi: 10.3390/medicina58070880. PMID: 35888598; PMCID: PMC9319431.

8 Feldman M, Goldschmiedt M. Gastric HCO3- secretion: relationship with Na^+ secretion and effect of acetazolamide in humans. Am J Physiol. 1991 Aug; **261**(2 Pt 1): G320–6. doi: 10.1152/ajpgi.1991.261.2.G320. PMID: 1872401.

9 Fischer JE. The pathophysiology of enterocutaneous fistulas. World J Surg. 1983 Jul; **7**(4): 446–50. doi: 10.1007/BF01655932. PMID: 6414189.

10 Galie KL, Whitlow CB. Postoperative enterocutaneous fistula: when to reoperate and how to succeed. Clin Colon Rectal Surg. 2006 Nov; **19**(4): 237–46. doi: 10.1055/s-2006-956446. PMID: 20011327; PMCID: PMC2780112.

11 Ghimire P. Management of Enterocutaneous Fistula: A Review. JNMA J Nepal Med Assoc. 2022 Jan 15; **60**(245): 93–100. doi: 10.31729/jnma.5780. PMID: 35199684; PMCID: PMC9157672.

12 Ghishan FK, Kiela PR. Small intestinal ion transport. Curr Opin Gastroenterol. 2012 Mar; **28**(2): 130–4. doi: 10.1097/MOG.0b013e32834e7bc3. PMID: 22157512; PMCID: PMC4427518.

13 Gribovskaja-Rupp I, Melton GB. Enterocutaneous Fistula: Proven Strategies and Updates. Clin Colon Rectal Surg. 2016 Jun; **29**(2): 130–7. doi: 10.1055/s-0036-1580732. PMID: 27247538; PMCID: PMC4882173.

14 Haack CI, Galloway JR, Srinivasan J. Enterocutaneous Fistulas: A Look at Causes and Management. Curr Surg Rep. 2014 Sep 16; **2**(10): 71. doi: 10.1007/s40137-014-0071-0.

15 Kelly DG, Nadeau J. Oral rehydration solution: A "low-tech" oft neglected therapy. Practical Gastroenterology. 2004; **28**: 51–62.

16 Kennedy HJ, Al-Dujaili EA, Edwards CR, Truelove SC. Water and electrolyte balance in subjects with a permanent ileostomy. Gut. 1983 Aug; **24**(8): 702–5. doi: 10.1136/gut.24.8.702. PMID: 6347830; PMCID: PMC1420234.

17 Lehmann A, Hornby PJ. Intestinal SGLT1 in metabolic health and disease. Am J Physiol Gastrointest Liver Physiol. 2016 Jun 1; **310**(11): G887–98. doi: 10.1152/ajpgi.00068.2016. Epub 2016 Mar 24. PMID: 27012770.

18 Loo DD, Wright EM, Zeuthen T. Water pumps. J Physiol. 2002 Jul 1; **542**(Pt 1): 53–60. doi: 10.1113/jphysiol.2002.018713. PMID: 12096049; PMCID: PMC2290409.

19 Medlin S. Nutritional and fluid requirements: high-output stomas. Br J Nurs. 2012 Mar 22-Apr 11; **21**(6): S22–5. doi: 10.12968/bjon.2012.21.Sup6.S22. PMID: 22584891.

20 Metcalf C. Considerations for the management of enterocutaneous fistula. Br J Nurs. 2019 Mar 14; **28**(5): S24–S31. doi: 10.12968/bjon.2019.28.5.S24. PMID: 30907655.

21 Nightingale JMD. How to manage a high-output stoma. Frontline Gastroenterol. 2021 Mar 22; **13**(2): 140–151. doi: 10.1136/flgastro-2018-101108. PMID: 35300464; PMCID: PMC8862462.

22 Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ. Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution, and glucose polymer electrolyte solution. Gut. 1992 Jun; **33**(6): 759–61. doi: 10.1136/gut.33.6.759. PMID: 1624155; PMCID: PMC1379331.

23 Pande RK, Gupta A. Gastrointestinal Stomas and Fistulas: What is Lost and What to Do? Indian J Crit Care Med. 2020 Sep; **24**(Suppl 4): S175–S178. doi: 10.5005/jp-journals-10071-23620. PMID: 33354037; PMCID: PMC7724941.

24 Papa A, Lopetuso LR, Minordi LM, Di Veronica A, Neri M, Rapaccini G, Gasbarrini A, Papa V. A modern multidisciplinary approach to the treatment of enterocutaneous fistulas in Crohn's disease patients. Expert Rev Gastroenterol Hepatol. 2020 Sep; **14**(9): 857–865. doi: 10.1080/17474124.2020.1797484. PMID: 32673498.

25 Parrish CR, DiBaise JK. Managing the Adult Patient With Short Bowel Syndrome. Gastroenterol Hepatol (N Y). 2017 Oct; **13**(10): 600–608. PMID: 29230136; PMCID: PMC5718176.

26 Shrimanker I, Bhattarai S. Electrolytes. 2023 Apr 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 31082167.

27 Singh O, Gupta S, Moses S, Jain DK. Spontaneous tubercular enterocutaneous fistula developing in the scar of a surgery done 14 years earlier. Saudi J Gastroenterol. 2009 Oct-Dec; **15**(4): 261–3. doi: 10.4103/1319-3767.56107. PMID: 19794273; PMCID: PMC2981844.

28 Tang QQ, Hong ZW, Ren HJ, Wu L, Wang GF, Gu GS, Chen J, Zheng T, Wu XW, Ren JA, Li JS. Nutritional Management of Patients With Enterocutaneous Fistulas: Practice and Progression. Front Nutr. 2020 Oct 6; **7**: 564379. doi: 10.3389/fnut.2020.564379. PMID: 33123545; PMCID: PMC7573310.

29 Tong CY, Lim LL, Brody RA. High output enterocutaneous fistula: a literature review and a case study. Asia Pac J Clin Nutr. 2012; **21**(3): 464–9. PMID: 22705439.

30 Weledji E. Perspectives on Enterocutaneous Fistula: A Review Article. Medical and Clinical Reviews. 2017; **3**: 5 doi: 10.21767/2471-299X.1000047.

31 Williams LJ, Zolfaghari S, Boushey RP. Complications of enterocutaneous fistulas and their management. Clin Colon Rectal Surg. 2010 Sep; **23**(3): 209–20. doi: 10.1055/s-0030-1263062. PMID: 21886471; PMCID: PMC2967321.

32 Wright H, Kearney S, Zhou K, Woo K. Topical Management of Enterocutaneous and Enteroatmospheric Fistulas: A Systematic Review. Wound Manag Prev. 2020 Apr; **66**(4): 26–37. doi: 10.25270/wmp.2020.4.2637. PMID: 32294057.