Medical Hypotheses 127 (2019) 66–70

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Can an amino acid-based oral rehydration solution be effective in managing immune therapy-induced diarrhea?

J.D. Hendrie, A. Chauhan, N.R. Nelson, L.B. Anthony*

University of Kentucky Markey Cancer Center, 800 Rose St., Lexington, KY 40536, USA

ARTICLE INFO

Keywords:
Immune therapy
Immune checkpoint inhibitors
Adverse events
Diarrhea
Colitis
Enterade
Amino acid
Supportive care

ABSTRACT

Immune checkpoint inhibitor (ICPi) therapy has transformed the way we treat cancer. However, its immune related adverse events (irAEs) can be debilitating and life threatening. Immune therapy-induced diarrhea (ITID) is one of the most commonly encountered irAEs and can lead to expensive and prolonged hospitalizations. The current standard of care for grade 3 or 4 ITID involves ICPi discontinuation, the initiation of steroids, and infliximab for refractory disease. This treatment regimen reverses the desired anti-tumor effect of ICPis, can lead to side effects, and is cost-ineffective. We report the first case of the successful treatment of grade 3 ITID with steroids and an amino acid-based oral rehydration solution (AA-ORS), enterade. Research suggests that AA-ORS may be used to reduce diarrhea and adequately hydrate patients, in contrast to glucose-based oral rehydration solutions, which have been implicated as a contributing factor to diarrhea in cancer patients. We hypothesize that an AA-ORS may mitigate ITID via safer and more economically viable means than the current standard of care, but more controlled trials are needed to test this hypothesis.

Introduction

Immune checkpoint inhibitors (ICPis), which led to the 2018 Nobel Prize in Physiology or Medicine [1], are monoclonal antibodies that inhibit immunosuppressive checkpoint protein-ligand interactions used by evasive tumor cells. These drugs target the programmed cell death-1 receptor (PD-1), its ligand (PD-1L), or the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) [2], as shown in Fig. 1. The relatively recent successes of these agents against various malignancies have established their routine use in patients with advanced disease [3–6]. As the use of ICPis increases, managing their immune related adverse events (irAEs) that affect the skin, lungs, liver, colon, and endocrine organs, though more rarely affecting the nervous, rheumatologic, and renal systems is important with regards to minimizing dosing interruption and/or attenuation [7,8]. While various studies have shown that combination therapy with a PD-1 inhibitor and CTLA-4 inhibitor e.g., nivolumab/ipilimumab has greater efficacy than monotherapy, it comes at the expense of increased risk to irAEs [9,10]. Gastrointestinal (GI) toxicity is among the most common irAEs [11] and can be debilitating if grade 3 or above (Table 1) [7,12,13]. It can range from mild, self-limiting diarrhea to ICPi-induced colitis necessitating hospitalization [14]. A phase III trial of combination nivolumab/ipilimumab for melanoma found GI toxicity in 15% of patients [15], while a recent 2018 systematic review of patients taking combination nivolumab/ipilimumab for melanoma showed the incidence of colitis to be 9–18% and diarrhea to be 34–45% [16].

Since irAEs are driven by non-specific T-cell activation and infiltration, treatment focuses on immunosuppression [14]. According to the 2018 American Society of Clinical Oncology clinical practice guidelines, the standard of care for grade 3 colitis is permanent CTLA-4 agent discontinuation and temporary cessation of PD-1 and PD-1L agents until patients recover to at least grade 1. For grade 4 colitis all ICPi treatment should be permanently discontinued. For both grade 3 and 4 colitis patients should be hospitalized for dehydration or electrolyte abnormalities and immediately receive corticosteroids. GI consult with appropriate workup (endoscopy, blood/stool testing, inflammatory markers, imaging) should be considered. Second line therapy with infliximab is recommended at 5–10 mg/kg within 2–3 days of symptoms refractory to corticosteroids [17]. However, therapy recommendations are unclear if symptoms persist despite treatment with infliximab [18]. There are multiple underlying drawbacks to this treatment approach. First, discontinuation of ICPis and subsequent immunosuppressant initiation reverses the desired immune-stimulatory anti-tumor effect and could allow malignancy progression. Second, corticosteroids and infliximab carry side effects. Corticosteroids are known to cause insomnia, hyperglycemia, mood disturbances,

* Corresponding author.
E-mail address: Lowell.anthony@uky.edu (L.B. Anthony).

https://doi.org/10.1016/j.mehy.2019.03.023
Received 25 January 2019; Accepted 26 March 2019
0306-9877/ © 2019 Elsevier Ltd. All rights reserved.

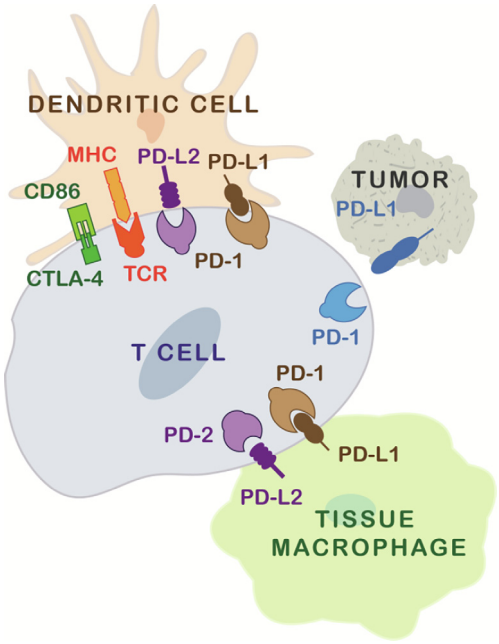


Fig. 1. Key immune checkpoint regulators involved in anti-tumor effects.

and a long taper to avoid altering the hypothalamic-pituitary-adrenal axis, while infliximab is associated with infusion site reactions, headache, and increased risk of infection. Third, although corticosteroids are relatively inexpensive, the cost of infliximab is quite substantial. According to REDBOOK Online, the wholesale acquisition cost of one 100 mg vial of infliximab is $1167.82 [19]. Given that 50% of patients with steroid-refractory colitis required multiple doses of infliximab [20], this therapy can be expensive. Therapy for an average 80 kg patient requiring two doses of infliximab at 10 mg/kg and $1167.82/100 mg vial would cost nearly $10,000. Future research must find avenues to not only mitigate irAEs, but to also do so through safer and more economically viable means.

Case report

Our patient was a 62-year-old female who originally presented to the University of Kentucky with neurologic deficits. Imaging revealed several brain masses, which prompted two craniotomies with parietal and temporal mass resections. Pathology confirmed malignant melanoma, but staging scans and dermatologic evaluation did not reveal disease elsewhere. Further genetic testing revealed the tumor was BRAF negative. Residual brain metastases were treated with gamma knife surgery. Medical oncology began adjuvant combination nivolumab/ipilimumab and our patient underwent two cycles of immunotherapy at a cancer facility closer to home. Following her second cycle, she developed moderate diarrhea and was started on a prednisone taper beginning at 60 mg daily. When her taper reached 15 mg daily, she presented to an outside hospital with worsening watery diarrhea, weight loss, extreme fatigue, and poor appetite. Loperamide and diphenoxylate/atropine were ineffective, but stool studies were negative and she was discharged. Nine days later she presented to the University of Kentucky Emergency Department with the same complaints. Since her discharge, she had consumed solely water and an over the counter (OTC) sports drink as her symptoms were exacerbated with food. Other symptoms included fever with chills and abdominal cramping. It had been roughly three weeks since her immunotherapy.

The patient was hemodynamically stable and physical exam was remarkable for an uncomfortable female with active bowel sounds and diffuse abdominal tenderness with a Karnofsky performance score of 60%. Stool studies were negative (Clostridium Difficile by PCR, comprehensive GI Panel by PCR, and Ova and Parasites). CT abdomen/pelvis revealed large and distal small bowel mural hyper-enhancement with fat stranding suggestive of chemotherapy related colitis/enteritis. The working diagnosis was grade 3 ICPi-induced colitis based on her severe abdominal pain and diarrhea necessitating hospitalization. No other irAEs had been found or reported.

Methylprednisolone 2 mg/kg IV daily was initiated on hospital day 1 (Fig. 2). Loperamide was continued initially, and her diarrhea (Type 7 Bristol Stool Scale) began to improve. Due to persistent diarrhea despite loperamide and diphenoxylate/atropine, anti-diarrheal agents were discontinued on day 4 to better assess the patient's stool burden, which worsened the patient's diarrhea. On hospital day 5 she experienced increased stools associated with abdominal pain, food restriction, and continued marked fatigue. On hospital day 6 the patient was started on enterade, an amino acid-based oral rehydration solution (AA-ORS), twice daily. Within 24 h her stools were of greater consistency (Type 6 Bristol Stool Scale) and decreased in frequency. After 72 h on enterade her stools were formed (Type 5 Bristol Stool Scale) at two bowel movements per day. Her abdominal pain and bloating resolved, her appetite increased, and she became ambulatory. On hospital day 9 she was discharged on prednisone and one 8 oz. bottle of enterade twice daily.

Discussion

Chemotherapy and radiation injury to the gastrointestinal mucosa occurs at the functional and structural levels. The damage often causes reduced electrolyte and nutrient absorption, increased paracellular permeability, translocation of bacterial products, mucositis, diarrhea, and dehydration [21,22]. Glucose-based oral rehydration solutions (G-ORS) were designed based on the sodium-coupled glucose transporter-1 (SGLT1) as it was well established that sodium and water absorption were stimulated by glucose. However, despite correcting dehydration and metabolic acidosis, G-ORS was shown to have minimal clinical benefit in reversing acute diarrhea [23]. In fact, it was postulated that in those with GI mucosal damage, the osmotic activity of unabsorbed glucose in the lumen actually worsened diarrhea [24]. Based on further research the World Health Organization released updated guidelines in 2006, advocating for the use of reduced osmolarity oral rehydration solutions that decrease stool output by avoiding glucose-induced hypertonicity [25]. More recent research has shown that glucose also induces calcium-activated chloride secretion into the gastrointestinal lumen, which coupled with glucose malabsorption secondary to cancer therapy-induced villous atrophy, explains why G-ORS has had modest success at best [23]. Considering that our patient's only oral intake prior to admission was water and an OTC sports drink (G-ORS), it warrants consideration that the aforementioned mechanism played a role in her ongoing diarrhea in addition to immune-related GI toxicity.

Along with glucose, amino acids are known to stimulate sodium and water absorption [26,27]. A recent study showed that a mixture of lysine, aspartic acid, glycine, isoleucine, threonine, tyrosine, valine, tryptophan, and serine increased electrolyte absorption while decreasing paracellular permeability and plasma endotoxins in patients with radiation-induced GI toxicity [28]. This added support to the concept that an AA-ORS could reduce diarrhea in patients undergoing cancer treatment.

Recent studies comparing AA-ORS and G-ORS have shown varied results. One group demonstrated that an AA-ORS led to greater fluid retention and interstitial volume restoration for hypertonic dehydration, in addition to superior electrolyte replacement and interstitial fluid volume preservation during isotonic dehydration compared to a G-ORS [29]. In contrast, another group's randomized clinical trial (NCT03262597) showed G-ORS to be slightly superior, although comparable to AA-ORS in optimizing hydration using the beverage hydration index [30]. It must be stated that neither study examined these effects in patients undergoing cancer treatment. Therefore, it remains

Downloaded for Anonymous User (n/a) at University of Kentucky from ClinicalKey.com by Elsevier on June 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

Table 1
National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (13).

	Grade				
CTCAE Term	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

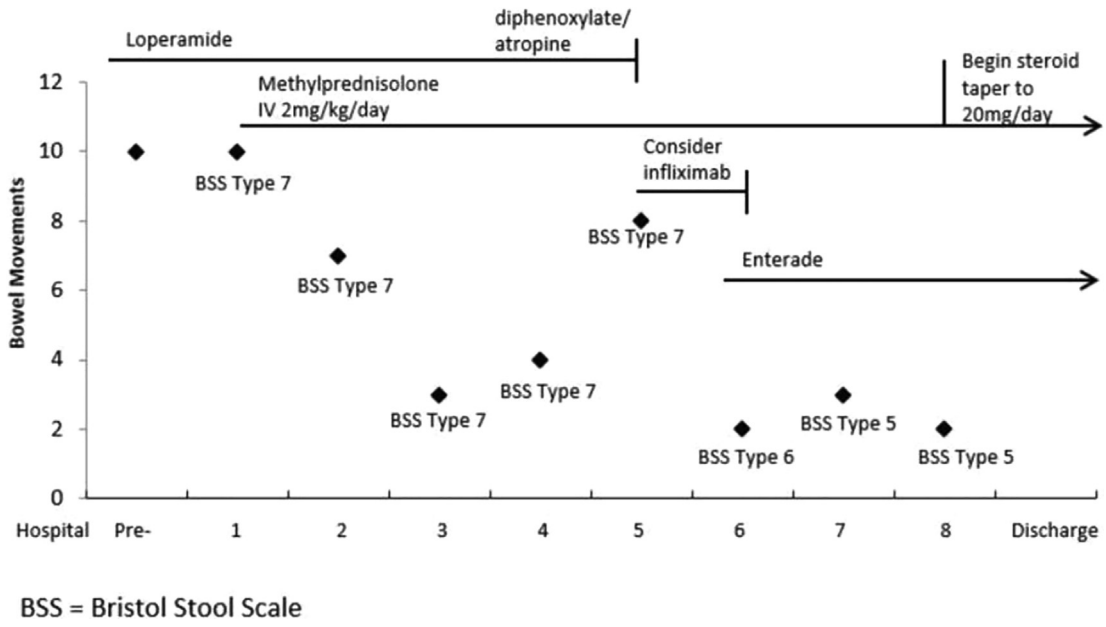


Fig. 2. Clinical course.

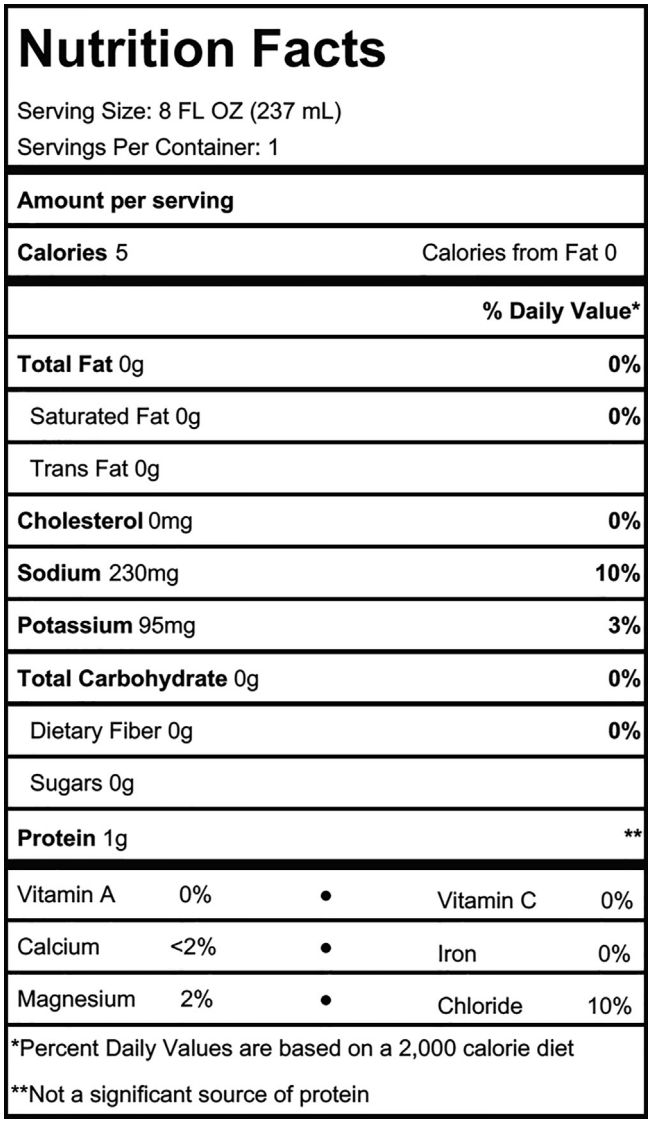
unclear whether AA-ORS or G-ORS shows superior efficacy in optimizing hydration status in cancer patients. We believe AA-ORS should be explored in cancer patients afflicted with diarrhea or dehydration secondary to cancer-related GI toxicity.

Enterade is a first-in-class, glucose-free amino acid-based oral rehydration solution with added electrolytes and natural sweetener. Enterade was developed by Dr. Vidyasagar at the University of Florida. Based on his preclinical in vivo data on irradiated mouse models, Dr. Vidyasagar demonstrated that enterade was able to treat dehydration and hence improve survival as compared to mice treated with normal saline and a random mixture of amino acid-based ORS [28]. This was later determined to be the result of gut regeneration, and further in vivo data confirmed that enterade increases crypt count and villus length, as well as sodium and chloride absorption [31]. Nutrition information can be found in Fig. 3. Since enterade is classified as a medical food, it is available without a prescription for about $5 per 8 oz. bottle. The recommended dose is two bottles per day, which must be taken 30 min before meals or one hour after. At present, there is only one active phase II trial studying its use in the treatment of diarrhea in neuroendocrine tumor patients (NCT03722511). Two other trials designed to study the use of enterade in patients with inflammatory bowel disease (NCT03451253) or short bowel syndrome (NCT03105362), respectively, are mentioned on clinicaltrials.gov, but their current status is unknown. A pilot study researching the anti-diarrheal efficacy of enterade in neuroendocrine tumor patients showed that 73.9% of patients reported improvement in diarrhea and 52.2% of patients reported a > 50% reduction in diarrhea frequency [32]. This prompted the design and registration of the aforementioned phase II clinical trial in neuroendocrine tumor patients, which is now open to accrual (NCT03722511).

Conclusion

Based on this anecdotal case report of a patient with grade 3 ICPi-induced colitis showing drastic improvement upon enterade initiation, we hypothesize that this AA-ORS may have benefit in patients being treated for immune therapy-induced diarrhea (ITID). Further controlled studies are needed to determine whether AA-ORS is effective in managing ITID. Developing supportive care agents that are non-toxic and inexpensive has the potential of significantly impacting outcomes given the risk of permanently discontinuing or interrupting effective ICPi therapy. The prompt treatment of grade ≥3 GI-irAEs via AA-ORS with or without corticosteroids would allow patients to resume their immunotherapeutic plan following symptom resolution, which is relevant for patients with limited treatment options. Also, the avoidance of prolonged corticosteroids and immunosuppressive therapy reduces the risk of side effects and opportunistic infections, while additionally allowing the continuation of the intended ICPi-induced anti-tumor effect. In addition, AA-ORS could significantly reduce patient and hospital costs. Even if combined with corticosteroids, solely forgoing infliximab could reduce overall expenses nearly 1000-fold. In conclusion, this report on the use of the AA-ORS, enterade, resulting in a positive outcome in a patient with grade 3 ICPi-induced colitis, coupled with the aforementioned potential benefits of AA-ORS suggest that this is a viable and cost-effective treatment option. Further ITID research is needed to improve the current treatment guidelines.

Downloaded for Anonymous User (n/a) at University of Kentucky from ClinicalKey.com by Elsevier on June 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.



Nutrition Facts

Serving Size: 8 FL OZ (237 mL)
Servings Per Container: 1

Amount per serving	
Calories 5	Calories from Fat 0
	% Daily Value*
Total Fat 0g	**0%**
Saturated Fat 0g	**0%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 230mg	**10%**
Potassium 95mg	**3%**
Total Carbohydrate 0g	**0%**
Dietary Fiber 0g	**0%**
Sugars 0g	
Protein 1g	**

Vitamin A	0%	•	Vitamin C	0%
Calcium	<2%	•	Iron	0%
Magnesium	2%	•	Chloride	10%

*Percent Daily Values are based on a 2,000 calorie diet

**Not a significant source of protein

Fig. 3. Enterade nutrition facts.

Sources of support in the form of grants

None to declare.

Conflicts of interest

The authors declare a research grant made payable to the University of Kentucky from Entrinsic Health Solutions for a phase II clinical trial. Dr. Chauhan declares a travel grant from Entrinsic Health Solutions for a research presentation.

Acknowledgements

The authors would like to thank Donna Gilbreath for her help with the design of the immune checkpoint inhibitor illustration (Fig. 1).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.03.023.

References

[1] Institutet TNAaK. The Nobel Prize in Physiology or Medicine 2018. < https://www.nobelprize.org/prizes/medicine/2018/press-release/ > ; 2018.
[2] Ventola CL. Cancer immunotherapy, Part 1: current strategies and agents. P & T J Formulary Manage 2017;42:375–83.
[3] Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018;378:2078–92.
[4] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.
[5] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.
[6] Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722–30.
[7] Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv119–42.
[8] Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer (Oxford England) 1990;54(2016):139–48.
[9] D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017;35:226–35.
[10] Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19:672–81.
[11] Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J ImmunoTher Cancer 2017;5:95.
[12] Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial Sloan Kettering Cancer Center. J Clin Oncol 2015;33:3193–8.
[13] United States Department of Health and Human Services., Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf; 2017.
[14] Wang Y, Abu-Sbeih H, Mao E, et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. J ImmunoTher Cancer 2018;6. pp. 37–37.
[15] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–56.
[16] Mearns ES, Bell JA, Galaznik A, et al. Gastrointestinal adverse events with combination of checkpoint inhibitors in advanced melanoma: a systematic review. Melanoma Manage 2018;5. pp. MMT01-MMT01.
[17] Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68.
[18] Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol 2017;8.
[19] Truven IWH. Health Analytics, Active ingredient: infliximab., Micromedex RED BOOK; 2018.
[20] Geukes Foppen MH, Rozeman EA, van Wilpe S, et al. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. ESMO Open 2018;3. pp. e000278–e000278.
[21] Khan SA, Wingard JR. Infection and mucosal injury in cancer treatment. JNCI Monographs 2001;2001:31–6.
[22] Beck PL, Wong JF, Li Y, et al. Chemotherapy- and radiotherapy-induced intestinal damage is regulated by intestinal trefoil factor. Gastroenterology 2004;126:796–808.
[23] Yin L, Vijaygopal P, MacGregor GG, et al. Glucose stimulates calcium-activated chloride secretion in small intestinal cells. Am J Physiol Cell Physiol 2014;306:C687–96.
[24] Gore SM, Fontaine O, Pierce NF. Impact of rice based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. BMJ (Clin Res ed.) 1992;304:287–91.
[25] Aboubaker S, Bhutta Z, Black RE, et al., Implementing the new recommendations on the clinical management of diarrhoea. http://apps.who.int/iris/bitstream/handle/10665/43456/9241594217_eng.pdf;jsessionid=BBD4B11A058794B86EB9FB664A6CD825?sequence=1; 2006, Accessed November 4 2018.
[26] Hellier MD, Thirumalai C, Holdsworth CD. The effect of amino acids and dipeptides on sodium and water absorption in man. Gut 1973;14:41–5.
[27] Silk DBA, Fairclough PD, Park NJ, et al. A study of relations between the absorption of amino acids, dipeptides, water and electrolytes in the normal human jejunum. Clin Sci 1975;49:401–8.
[28] Yin L, Vijaygopal P, Menon R, et al. An amino acid mixture mitigates radiation-induced gastrointestinal toxicity. Health Phys 2014;106:734–44.
[29] Cheuvront SN, Kenefick RW, Charkoudian N, et al. Efficacy of glucose or amino acid-based commercial beverages in meeting oral rehydration therapy goals after acute hypertonic and isotonic dehydration. JPEN J Parenteral Enteral Nutr

Downloaded for Anonymous User (n/a) at University of Kentucky from ClinicalKey.com by Elsevier on June 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

2018;42:1185–93.
[30] Sollanek KJ, Tsurumoto M, Vidyasagar S, Kenefick RW, Cheuvront SN. Neither body mass nor sex influences beverage hydration index outcomes during randomized trial when comparing 3 commercial beverages. Am J Clin Nutr 2018;107:544–9.
[31] Yin L, Gupta R, Vaught L, Grosche A, Okunieff P, Vidyasagar S. An amino acid-based oral rehydration solution (AA-ORS) enhanced intestinal epithelial proliferation in mice exposed to radiation. Sci Rep 2016;6:37220.
[32] Chauhan A, Yu Q, Miller RC, Luque L, Weiss H, Anthony LB. The antidiarrheal efficacy of a proprietary amino acid mixture (enterade) in neuroendocrine tumor (NET) patients. J Clin Oncol 2018;36. p. e22217–e22217.

Downloaded for Anonymous User (n/a) at University of Kentucky from ClinicalKey.com by Elsevier on June 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.