Case Study

High output enterocutaneous fistula: a literature review and a case study

Chung Yan Tong RD, CNSC[1], Li Lin Lim MRCP[2], Rebecca A Brody PHD, RD, CNSC[3]

[1]*Dieteitcs Department, National University Hospital, Singapore*
[2]*Department of Gastroenterology and Hepatology, National University Hospital, Singapore*
[3]*Department of Nutritional Sciences, School of Health Related Professions, University of Medicine and Dentistry of New Jersey, United States*

An enterocutaneous (EC) fistula is referred to as a channel between the gut and the skin. Effluent of an EC fistula of more than 500 ml per day is considered as high output. Patients with high output EC fistulae have a high morbidity and mortality rate. No evidence-based guidelines are available for this condition and more research is required to evaluate the effectiveness of treatment. Nevertheless, patients with fistulae should be managed based on the available evidence, detailed clinical and nutrition assessment, and close monitoring. Management of high output EC fistula is complex and challenging. It involves nutrition, medical, skin care and psychological treatment, which is best managed by a multidisciplinary team. It requires an individualized nutrition and clinical treatment plan to maximize patient outcomes. Up to 70% of patients with fistulae have malnutrition and it is a significant prognostic factor of spontaneous fistula closure. Nutrition therapies including macronutrient and micronutrient delivery, enteral nutrition and parenteral nutrition are discussed in this review. A case study of a patient with multiple EC fistulae is presented to illustrate the management of high output EC fistulae.

Key Words: intestinal fistula, cutaneous fistula, parenteral nutrition, enteral nutrition, intestinal secretions

INTRODUCTION

Fistula is defined as an abnormal communication of an organ to another organ, skin or wound.[1,2] If a fistula is between the gut and another part of the body, it is generally called a gastrointestinal (GI) fistula.[1] An enterocutaneous (EC) fistula is referred to as a channel between the gut and the skin.[2] The pathophysiology of fistulae can be explored through various techniques, including the methylene blue test, fistulography, computed tomography scan, ultrasonography, magnetic resonance imaging and endoscopy.[2]

Surgery accounts for 75% to 85% of gastrointestinal fistula development and the fistula usually arises five to ten days after an operation.[3] It is likely to happen in emergency surgery when pre-operative preparation is usually poor.[1] For spontaneous fistula development, Crohn's disease is the major cause and 40% of this group develops fistula.[2] Effluent of an EC fistula of more than 500ml per day is considered as high output. Patients with high output EC fistulae have a high morbidity and mortality rate.[1] This review focuses on high output EC fistulae.

LITERATURE REVIEW ON FISTULA MANAGEMENT

Prognosis of a GI fistula depends on the patient characteristics, nutritional status, fistula characteristics and other co-morbidities.[4-6] The endpoint of GI fistula is fistula closure, either spontaneously or surgically. Table 1 summarizes the factors that may cause delay in spontaneous fistula closure and Table 2 summarizes the management of GI fistula based on literature review.

Overall, management of high output EC fistula is complex and challenging. It involves nutrition, medical, skin care and psychological treatment. A case study of a patient with multiple EC fistulae is presented to illustrate the management of high output EC fistulae.

CASE STUDY PRESENTATION

JY, is a 23-year-old Chinese female, admitted to the hospital due to a serious motorcycle accident. She suffered haemoperitoneum with a mesenteric tear at the ileum, sigmoid colon and caecum. JY had resection of ischemic parts of the gut in the first two days of admission. On hospital day 25, a serosal tear of small bowel was noted and surgical repair was done (Table 3). The initial defect had increased in size and a new defect was found 3 days later. Her small bowel was extremely frail to any suturing. On hospital day 37, a third small bowel defect had developed, and small bowel endoscopic stenting was attempted to repair the fistulae but this was unsuccessful. On hospital day 40, the most proximal fistula had increased to 4

Corresponding Author: Ms. Chung Yan Tong, National University Hospital, Dietetics Department, Main Building, Level 1, 5 Lower Kent Ridge Road, Singapore 119074.
Tel: (65)67725166; Fax: (65)67791938
Email: cherie_tong@nuhs.edu.sg
Manuscript received 22 September 2011. Initial review completed 17 January 2012. Revision accepted 5 March 2012.

Table 1. Factors that may cause delay in spontaneous fistula closure [1,2,4-6]

Old age >65 Malnutrition Organ involved: stomach, duodenum, ileum. Fistula duration >4-6 weeks. Fistula output >500 ml/day. Etiology of fistula: malignancy, inflammatory bowel disease, radiation enteritis Co-morbidities: sepsis, diabetes or renal failure, under chemotherapy, radiation or corticosteroid treatment.	Fistula presentation: External, complex, multiple or end fistula. Fistula tract <2 cm or defect >1 cm. Eversion of mucosa or distal occlusion. Poor or diseased adjacent bowel. Presence of abscess or foreign body. Presence of abdominal wall defect. Management errors: failure to diagnose an anastamotic leak, a delay in surgical exploration, attempt to restore intestinal continuity too early and failure to initiate nutrition support.

Table 2. Management of gastrointestinal (GI) fistula based on literature review [1-34]

Goals	To prevent complications, promote spontaneous closure and minimize morbidity and mortality.[1-4]
Multidisciplinary approach	A gastroenterologist, surgeon, radiologist, nutrition support dietitian, wound ostomy nurse, pharmacist and psychologist.[7,8]
Fluid & electrolyte management	Active replacement to prevent dehydration, electrolyte imbalance (eg, hyponatremia, hypokalemia) and metabolic acidosis or alkalosis.[2,9,10]
Nutrition assessment	Up to 70% of patients with fistulae have malnutrition and it is a significant prognostic factor for spontaneous fistula closure. Baseline and regular nutrition assessment is fundamental.[1,2,9,19-21]
Enteral nutrition	Preferred route of nutrition support, unless it causes significantly increased fistula output, abdominal pain or diarrhea.[9,22,23]
Oral diet	High sodium, low residue diet and use of oral rehydration solutions to replace fistula losses.[1,15,33]
Fistuloclysis	1) delivering feed via the fistula site by inserting a tube under radiology into the fistula; 2) feeding the fistula effluent from the proximal fistula to the distal fistula.[16,34]
Parenteral nutrition	Individualized parenteral nutrition regimen should be planned to meet nutrition, fluid and electrolyte requirements and to minimize PN-related complications (eg, hyperglycemia, bacterial translocation, catheter sepsis, vein thrombosis, cholestasis, steatosis and metabolic bone disease).[10,23-30]
Nutritional Requirements	Low output GI fistula:[1] Resting energy expenditure (REE) or 25 kcal/kg body weight/day, 1.0-1.5 g protein/kg body weight/day. High output GI fistula:[1] 1.5 x REE or 30 kcal/kg body weight/day,1.5-2.0 g protein/kg body weight/day, 2 x daily recommended intake (DRI) of vitamins and trace minerals, 5 x DRI of vitamin C and zinc. At risk of vitamin B12, zinc, magnesium and selenium deficiency.[15,33]
Medications	To reduce gut motility and digestive secretion: somatostatin and its analog (Octeotide), loperamide, diphenoxylate, codeine, opium tincture, stress ulceration prophylaxis (eg, proton pump inhibitors and H_2 receptor antagonist).[1,4,11-16]
Artificial fistula closure	Using fibrin glue via fistuloscopy, stenting via endoscopy, surgical fistula closure (at least three months after the patient has been hemodynamically stable with adequate nutritional support to maximize the chance of a successful surgery).[1,2,4-6,9,11-18]

cm. Dense adhesions were found in the intestines and other organs described by the surgeons as like a 'cocoon.'

JY was on parenteral nutrition (PN) and antibiotic treatment for persistent intrabdominal sepsis for the following 6 months (Tables 3 and 4). The output from the proximal fistula remained very high, ranging from 1.6-4.6 L/day. When she developed line sepsis eight months after admission, the surgeon operated on her to close the three fistulae. One week after the operation, a new small jejunum perforation was found and repaired. However, this new defect formed a small fistula with moderate output of 200 – 400ml per day. She was started on an oral diet and she remained an inpatient for another three months for antibiotic treatment and rehabilitation. She was discharged ten months after admission. She had her stoma dressing done at a nearby clinic on a weekly basis and had monthly follow-up appointments with the surgeon, the dietitian and the wound ostomy nurse in the hospital.

NUTRITION MANAGEMENT

Baseline nutrition assessment was performed using the Subjective Global Assessment (SGA) according to weight history, dietary intake change, GI symptoms, functional capacity, disease state and physical exams.[35] The SGA rating was A which implied JY was well nourished at admission. SGA was performed every 3 months and JY's SGA rating dropped to B (moderately malnourished) in the third to sixth month due to multiple infections, reiterated surgery and persistent high fistulae output despite ongoing PN support. JY remained moderately malnour-

ished at discharge but her nutritional status gradually improved with increased oral intake, reduced fistula output and the absence of infection.

Electrolyte levels and fluid balance were monitored closely. The PN regime was adjusted and intravenous electrolyte replacement was given accordingly (Table 4). Her serum sodium, potassium and magnesium levels were depleted initially when the fistula output was more than 2L/day. The maximum compatible dose of magnesium and zinc were prescribed in the PN solution and intravenous zinc supplementation was given to JY daily while she was on PN to compensate for her losses through the high output EC fistulae.

The amount of fistula output was associated with her oral diet consumption; her fistula output increased up to 4L/day when she had good oral intake in the third, sixth and seventh month post injury (Table 3). The output reduced to 1.2-1.8 L/day when her appetite was poor in the fourth and fifth months of hospitalization. She refused oral rehydration solution, semi-elemental and elemental supplements. Her poor dietary compliance was likely due to depression caused by the long hospital stay, chronic forearm wound, high output fistulae and financial concern. JY did not tolerate fistuloclysis with fistula effluent. Somatostatin was prescribed twice for a duration of 3 weeks each and it reduced the fistula output to approximately 1L per day.

Folate, vitamin B-12, zinc and an iron panel were monitored in the third month. Her folate, vitamin B-12 and zinc levels were normal. Her iron, total iron binding capacity, and transferrin were low with elevated ferritin indicating chronic disease and repeated operation-related acute blood loss. JY received regular blood transfusions when her hemoglobin was low after each operation.

Parenteral nutrition was the major source of nutrition support for JY with a total of 229 days of PN during her hospital stay. She suffered cholestasis and steatosis three months after PN started. Cyclic PN of 16 hours was

Table 3. JY's weight trend, laboratory data, fistula output and nutrition support regime

Hospital Stay (month)	Weight (kg)	Pertinent Laboratory Data†	Key Medial Events	Fistula Output (L/day)	Nutrition Support Regime‡
1	55	BUN: 50-120 mg/dL Cr: 22 mg/dL Glu: 150-200 mg/dL Alb: 15-25 g/L LFT: normal TG: normal	Major operations at right forearm and abdomen. Formation of 3 EC fistulae. Stayed in intensive care unit.	0-0.2	Oral: Nill by mouth. PN: initial regime in Table 4 with standard MVI and trace element. Enteral feeding was initiated in ICU and discontinued when small bowel perforated.
3	52	Na: 132-137 mmol/L K: 3-4.5 mmol/L Mg: 0.79-0.94 mmol/L Glu: 85-175 mg/dL Alb: 26-31 g/L ALT: 34-129 U/L ALP: 272-549 U/L GGT: 362 U/L Bil: 11-22 μmol/L TG: 237-356 mg/dL	Started somatostatin for 3 weeks in view of very high fistula output. JY was very depressed and she was allowed to have oral diet.	1.6-4.0	Cyclic PN: 16 hours. Reduce lipid infusion to x 2/week. Addition IV zinc: 5 mg/day. Trial of SMOF lipid. Oral: Refused ORS, semi-elemental and elemental feed, educated on high protein, low residue diet but with poor diet compliance. Electrolyte replacement:IV K and Mg.
6	53-55	Glu: 126-128 mg/dL K: 3.6-4.6 mmol/L Mg: 0.45-0.93 mmol/L ALT: 14-93U/L ALP: 167-498 U/L GGT: 89-306 U/L Bil: 2-8 μmol/L TG: 90-182 mg/dL	Discontinued somatostatin due to high cost and unlikely spontaneous fistula closure. Line sepsis occurred at the end of 7th month. JY was encouraged to increase oral intake.	2.1-4.6	PN: discontinued at the end of 7th months due to line sepsis. Oral: Normal diet with increased intake, poor diet compliance, refused ORS, small amount of semi-elemental feed and some standard oral supplements. JY lost 2 kg in 2 weeks when PN was off.
9	53	Glu: 104-135 mg/dL K: 3.0-4.6 mmol/L Mg: 0.60-1.00 mmol/L ALT: 29-93U/L ALP: 199-585 U/L GGT: 123-400 U/L Bil: 10-58 μmol/L TG: 192-276 mg/dL	Small bowel fistulae closure, adhesiolysis and took down colostomy. New small jejunal fistula formed with moderate output.	0.2-1.7	PN: restarted after fistula closure with same previous regime, weaned off in middle of 9th month when oral intake increased with moderate fistula output. Electrolyte replacement: IV K and Mg Oral: as above.

† Abbreviation: full text (normal range):
BUN: blood urea nitrogen (12-39 mg/dL), Cr: serum creatinine (5.5-9.9 mg/dL), Na: serum sodium (135-150 mmol/L), K: serum potassium (3.5-5.0 mmol/L), Glu: blood glucose (72-140 mg/dL), Mg: magnesium (0.75-1.07 mmol/L), Alb: serum albumin (38-48 g/L), LFT: liver function test, ALT: alanine transaminase (10-70 U/L), ALP: alkaline phosphatase (40-130 U/L), GGT: gamma-glutamyltransferase (10-80 U/L), Bil: total bilirubin (5-30 μmol/L) , TG: triglyceride (<150 mg/dL)
‡ MVI: multivitamin infusion, SMOF: soybean oil, medium chain triglycerides, olive oil and fish oil, ORS: oral rehydration solution. IV: intravenous infusion

Table 4. JY's nutrition management plan

Nutrition Goals:	Estimated nutrition requirements:
1. maintain nutritional status by delivering adequate energy and nutrients 2. provide sufficient protein for skin integrity and replacing losses from fistula output 3. maintain fluid balance and normalize electrolytes 4. facilitate wound healing and fistula closure 5. prevent and promote recovery from infection and sepsis 6. prevent vitamin and mineral deficiencies 7. prevent parenteral nutrition related complications.	Admission weight: 55 kg Height: 1.6 m BMI: 22 kg/m^2 Energy: 30 kcal/kg/day = 1650 kcal/day Protein: 1.5 g/kg body weight/day = 83 g/day Aim for fluid balance: urine output, fistula output, drainage, blood loss etc. Vitamin and minerals: DRI levels

Parenteral nutrition (PN) prescription (per day)						
Type of PN	Calories kcal (kcal/kg)	Protein g (g/kg)	Dextrose g (g/kg)	Lipid g (g/kg)	Magnesium mmol (mmol/kg)	Zinc mg (mg/kg)
Initial	1678 (31)	90 (1.64)	270 (4.9)	40 (0.73)	13 (0.24)	11.5 (0.21)
Cyclic	1532 (28)	125 (2.27)	270 (4.9)	40x2/wk (0.73)	15 (0.27)	11.5+5 (IV) = 16.5(0.3)

arranged and lipid infusion was decreased to twice a week. Metronidazole was prescribed to treat possible bacterial overgrowth which may have compromised her liver function. Her total bilirubin level improved but the liver function test (LFT), gamma-glutamyltransferase (GGT) and triglyceride (TG) levels remained high (Table 3). Soybean oil, medium chain triglycerides, olive oil and fish oil (SMOF) lipid (SMOFlipid®, Fresenius Kabi) was used in her PN formulation in the fourth month and reductions of LFT, GGT and TG were observed. When PN was stopped due to line sepsis, the LFT and GGT returned to normal ranges. Parenteral nutrition-associated liver disease (PNALD) was evident because LFT, GGT, TG and total bilirubin levels were elevated again when PN was restarted after the fistulae closure operation.

Upon discharge, JY was educated about the optimal oral diet to maintain her weight and nutritional status. She was advised on sufficient fluid intake and how to monitor her hydration status. She was also discharged with oral potassium, magnesium and iron supplements.

CONCLUSIONS

This case study illustrates that high output EC fistula is a complex, demanding condition which is best managed by a multidisciplinary team. Not only does it have a high morbidity and mortality rate, it also has a significant financial and psychological impact. It requires an individualized nutrition and clinical treatment plan to maximize patient outcomes. More research is required to evaluate the effectiveness of treatment and to develop evidence-based guidelines. Meanwhile, patients with fistulae should be managed based on the available evidence, detailed clinical and nutrition assessment, and close monitoring.

AUTHOR DISCLOSURES

The authors do not have any financial support or relationships that may pose a conflict of interest. The authors also do not have any industrial links and affiliations.

REFERENCES

1. Cozzaglio L, Farinella E, Bagnoli P, Sciannameo F, Doci R. Gastrointestinal fistulas. Nutr Ther Metabol. 2007;25:113-34.
2. Lloyd DAJ, Gabe SM, Windsor ACJ. Nutrition and management of enterocutaneous fistula. Br J Surg. 2006;93: 1045-55.
3. Berry SM, Fischer JE. Classification and pathophysiology of enterocutaneous fistulas. Surg Clin North Am. 1996;76: 1009-18.
4. Campos AC, Andrade DF, Campos GM, Matias JE, Coelho JC. A multivariate model to determine prognostic factors in gastrointestinal fistulas. J Am Coll Surg. 1999;188:483-90.
5. Hollington P, Mawdsley J, Lim W, Gabe SM, Forbes A, Windsor AJ. An 11-year experience of enterocutaneous fistula. Br J Surg. 2004;91:1646-51.
6. Haffejee AA. Surgical management of high output enterocutaneous fistulae: a 24-year experience. Curr Opin Clin Nutr Metab Care. 2004;7:309-16.
7. Datta V, Engledow A, Chan S, Forbes A, Cohen CR, Windsor A. The management of enterocutaneous fistula in a regional unit in the United kingdom: a prospective study. Dis Colon Rectum. 2010;53:192-9.
8. McNaughton V, Canadian Association for Enterostomal Therapy ECF Best Practice Recommendations Panel, Brown J, Hoeflok J, Martins L, McNaughton V, Nielsen EM, Thompson G, Westendorp C. Summary of best practice recommendations for management of enterocutaneous fistulae from the Canadian Association for Enterostomal Therapy ECF Best Practice Recommendations Panel. J Wound Ostomy Continence Nurs. 2010;37:173-84.
9. Willcutts K, Eddins C. Ostomies and fisulas: a collaborative approach. Pract Gastroenterol. 2005;33:65-79.
10. Gonzalez-Pinto I, Gonzalez EM. Optimising the treatment of upper gastrointestinal fistulae. Gut. 2001;49(S4):iv22-31.
11. Martineau P, Shwed JA, Denis R. Is octreotide a new hope for enterocutaneous and external pancreatic fistulas closure? Am J Surg. 1996;172:386-95.
12. Alivizatos V, Felekis D, Zorbalas A. Evaluation of the effectiveness of octreotide in the conservative treatment of postoperative enterocutaneous fistulas. Hepatogastroenterology. 2002;49:1010-2.
13. Leandros E, Antonakis PT, Albanopoulos K, Dervenis C, Konstadoulakis MM. Somatostatin versus octreotide in the treatment of patients with gastrointestinal and pancreatic fistulas. Can J Gastroenterol. 2004;18:303-6.
14. Hesse U, Ysebaert D, de Hemptinne B. Role of somatostatin-14 and its analogues in the management of gastrointestinal fistulae: clinical data. Gut. 2001;49(S4): iv11-21.
15. Buchman AL. Short-bowel syndrome. Clin Gastroenterol Hepatol. 2005;3:1066-70.

16. Willcutts K. The Art of Fistuloclysis: Nutritional Management of Enterocutaneous Fistulas. Pract Gastroenterol. 2010;87:47-56.
17. Lynch AC, Delaney CP, Senagore AJ, Connor JT, Remzi FH, Fazio VW. Clinical outcome and factors predictive of recurrence after enterocutaneous fistula surgery. Ann Surg. 2004;240:825-31.
18. Conter RL, Roof L, Roslyn JJ. Delayed reconstructive surgery for complex enterocutaneous fistulae. Am Surg. 1988;54:589-93.
19. Windsor JA, Hill GL. Protein depletion and surgical risk. Aust N Z J Surg. 1988;58:711-5.
20. Windsor JA, Hill GL. Risk factors for postoperative pneumonia. The importance of protein depletion. Ann Surg. 1988;208:209-14.
21. Reilly JJ, Jr., Hull SF, Albert N, Waller A, Bringardener S. Economic impact of malnutrition: a model system for hospitalized patients. JPEN J Parenter Enteral Nutr. 1988; 12:371-6.
22. Meguid MM, Campos AC. Nutritional management of patients with gastrointestinal fistulas. Surg Clin North Am. 1996;76:1035-80.
23. Levy E, Frileux P, Cugnenc PH, Honiger J, Ollivier JM, Parc R. High-output external fistulae of the small bowel: management with continuous enteral nutrition. Br J Surg. 1989;76:676-9.
24. Campos AC, Meguid MM, Coelho JC. Factors influencing outcome in patients with gastrointestinal fistula. Surg Clin North Am. 1996;76:1191-8.
25. Dudrick SJ, Maharaj AR, McKelvey AA. Artificial nutritional support in patients with gastrointestinal fistulas. World J Surg. 1999;23:570-6.
26. Rombeau JL, Rolandelli RH. Enteral and parenteral nutrition in patients with enteric fistulas and short bowel syndrome. Surg Clin North Am. 1987;67:551-71.
27. Alexander JW. Bacterial translocation during enteral and parenteral nutrition. Proc Nutr Soc. 1998;57:389-93.
28. Sedman PC, MacFie J, Palmer MD, Mitchell CJ, Sagar PM. Preoperative total parenteral nutrition is not associated with mucosal atrophy or bacterial translocation in humans. Br J Surg. 1995;82:1663-7.
29. Zera RT, Bubrick MP, Sternquist JC, Hitchcock CR. Enterocutaneous fistulas. Effects of total parenteral nutrition and surgery. Dis Colon Rectum. 1983;26:109-12.
30. Deitel M. Elemental diet and enterocutaneous fistula. World J Surg. 1983;7:451-4.
31. American Dietetic Association. American Dietetic Association Evidence Analysis Library. [cited 2011/7/15]; Available from: http://www.adaevidencelibrary.com
32. Essential Evidence Plus. [cited 2011/7/15]; Available from: http://www.essentialevidenceplus.com.libproxy.umdnj.edu/content/
33. Buchman AL. Etiology and initial management of short bowel syndrome. Gastroenterology. 2006;130(2 Suppl 1): S5-S15.
34. Teubner A, Morrison K, Ravishankar HR, Anderson ID, Scott NA, Carlson GL. Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. Br J Surg. 2004;91: 625-31.
35. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11:8-13.

Case Study

High output enterocutaneous fistula: A literature review and a case study

Chung Yan Tong RD, CNSC[1], Li Lin Lim MRCP[2], Rebecca A Brody PHD, RD, CNSC[3]

[1]*National University Hospital, Singapore*
[2]*Department of Gastroenterology and Hepatology, National University Hospital, Singapore*
[3]*Department of Nutritional Sciences, School of Health Related Professions, University of Medicine and Dentistry of New Jersey, United States*

高流量肠外瘘：文献回顾及病例研究

肠外瘘是指肠道和皮肤之间的通道。如果肠外瘘每日排出超过五百毫升便被视为高流量肠外瘘。高流量肠外瘘患者的患病和死亡的机率很高。目前没有以科研证据为基础的肠外瘘医疗指引，而需要更多的研究以评估治疗的有效性。然而，肠外瘘患者的治疗应根据现有的科研证据，详细的临床和营养评估，并密切监测管理来拟定。高流量肠外瘘的治疗是复杂和具有挑战性的。它涉及到营养、医学、皮肤护理和心理治疗。这需由不同专业医疗小组依据个别状况来拟定一个适合病患的营养和临床治疗方案，才能达到最佳的治疗效果。高达七十百分比的肠外瘘患者患有营养不良，而营养不良是预测肠外瘘自发愈合的一个重要因素。本篇回顾所要讨论的营养治疗包括：主要营养素及微量营养素的供給，肠内营养和肠外营养辅助。本文将以一个患有多重肠外瘘病人的个案来说明高流量肠外瘘的管理。

关键词：肠瘘、皮肤瘘、肠外营养、肠内营养、肠分泌