

What is the effectiveness of Octreotide in the management of enteric and pancreatic fistula?

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SUMMARY STATEMENT:

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REQUEST:

What is the effectiveness of Octreotide in the management of enteric and pancreatic fistula?

REQUESTED BY:

Dr Stephen Blamey, General Surgery, Surgical Gastroenterology and Endoscopy, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Search question:

Patients: Those with enteric or gastric fistula

Intervention: Octreotide

Comparison: All others

Outcomes: Any

Search terms:

The following search terms were used to scour electronic databases and websites:

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient-related	Enteric fistula, enteral fistula, digestive system fistula, small bowel fistula, intestin/e/es/al fistula, pancrea/s/tic fistula
Intervention-related	Octreotide, sandostatin/e

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library CD-ROM- Issue 3 2000
- Best Evidence (OVID)- 1991 to September/ October 2000
- Medline (OVID)-1966 to December Week 4, 2000
- CINAHL (OVID)- 1982 to October 2000
- Current Contents (OVID)- 1993 Week 26 to 2000 Week 47
- Pre-Medline- November 22, 2000
- Journals@ Ovid Fulltext- November 22, 2000
- Turning Research into Practice (TRIP)- November 22, 2000
- National Guideline Clearinghouse- November 22, 2000
- Australasian Medical Index- November 22, 2000
- Micromedex DRUGEX- November 22, 2000

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 22 November, 2000. Critical appraisal was performed on the subset of studies published in English.

RESULTS:

From our sources we identified 94 articles which we categorised as follows:

Table 2. Study designs of articles retrieved by search

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	3
Controlled trials, cohort or case-control analytic studies	excluded
Descriptive case series	excluded
Consensus reports, non-evidence-based clinical practice guidelines	excluded
Narrative reviews	excluded

Articles were excluded from further appraisal as follows:

Table 3. Reasons for exclusion of articles retrieved by search

Reason for exclusion	Number
Level III evidence	2
Level IV evidence	45
Prophylaxis not treatment	15
Non-English	23

We are reasonably confident these articles represent the most important findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

1. National Health and Medical Research Council. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: Commonwealth of Australia, 1999.

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

- Nubiola-Calonge, P., J. M. Badia, et al. (1987). "Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output." Lancet **2**(8560): 672-4.
- Sancho, J. J., J. di Costanzo, et al. (1995). "Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula [see comments]." British Journal of Surgery **82**(5): 638-41.
- Scott, N. A., S. Finnegan, et al. (1993). "Octreotide and postoperative enterocutaneous fistulae: a controlled prospective study." Acta Gastroenterologica Belgica **56**(3-4): 266-70.

ARTICLES NOT CRITICALLY APPRAISED

Level III evidence

- Alvarez, C., D. W. McFadden, et al. (2000). "Complicated enterocutaneous fistulas: failure of octreotide to improve healing." World Journal of Surgery **24**(5): 533-7; discussion 538.
- Sitges-Serra, A., X. Guirao, et al. (1993). "Treatment of gastrointestinal fistulas with Sandostatin." Digestion **54**(Suppl 1): 38-40.

Level IV evidence

- Anonymous (1997). "Summary: Mexican Consensus on the Integral Management of Digestive Tract Fistulas." Nutrition **15**(3): 235-38.
- Ayache, S. and R. G. Wadleigh (1999). "Treatment of a malignant enterocutaneous fistula with octreotide acetate." Cancer Investigation **17**(5): 320-1.
- Barnes, S. M., B. G. Kontny, et al. (1993). "Somatostatin analog treatment of pancreatic fistulas." International Journal of Pancreatology **14**(2): 181-8.
- Bassi, C., M. Falconi, et al. (1996). "Somatostatin analogues and pancreatic fistulas." Digestion **57**(Suppl 1): 94-6.
- Bassi, C., M. Falconi, et al. (2000). "Role of octreotide in the treatment of external pancreatic pure fistulas: a single-institution prospective experience." Langenbecks Archives of Surgery **385**(1): 10-3.
- Boike, G. M., S. E. Sightler, et al. (1992). "Treatment of small intestinal fistulas with octreotide, a somatostatin analog." Journal of Surgical Oncology **49**(1): 63-5.
- Carlson, G. L., N. A. Scott, et al. (1994). "Somatostatin in gastroenterology. More studies needed [letter; comment]." Bmj **309**(6954): 604-5.
- Chan, K. L., W. Y. Lau, et al. (1994). "Octreotide therapy for pancreaticopleural fistula." Journal of Gastroenterology & Hepatology **9**(5): 530-2.
- Chen, R. J., J. F. Fang, et al. (1992). "Octreotide in the management of postoperative enterocutaneous fistulas and stress ulcer bleeding." American Journal of Gastroenterology **87**(9): 1212-5.
- Cooper, M. M., F. H. Wright, et al. (1989). "Successful treatment of a high-output fistula with a somatostatin analogue following pancreas transplantation." Transplantation Proceedings **21**(4): 3738-41.

- Curtin, J. P. and L. L. Burt (1990). "Successful treatment of small intestine fistula with somatostatin analog." Gynecologic Oncology **39**(2): 225-7.
- Dorta, G. (1999). "Role of octreotide and somatostatin in the treatment of intestinal fistulae." Digestion **60**(Suppl 2): 53-6.
- Falconi, M., N. Sartori, et al. (1999). "Management of digestive tract fistulas. A review." Digestion **60**(Suppl 3): 51-8.
- Fielding, G. A., O. J. Garden, et al. (1988). "Treatment of pancreatic fistula [letter]." British Journal of Surgery **75**(10): 1044.
- Frick, T. (1996). "Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis [letter; comment]." British Journal of Surgery **83**(3): 422-3.
- Grauer, L. and J. S. Barkin (1994). "Role of somatostatin and octreotide in the treatment of pancreatic pseudocyst, fistula and ascites." Digestion **55**(Suppl 1): 24-8.
- Gullo, L., G. Biliotti, et al. (1991). "Effect of octreotide (SMS 201-995) on meal-stimulated pancreatic secretion in three patients with external pancreatic fistula." American Journal of Gastroenterology **86**(7): 892-4.
- Jenkins, S. A., P. Javle, et al. (1995). "Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula [letter; comment]." British Journal of Surgery **82**(11): 1576.
- Jenkins, S. A., D. M. Nott, et al. (1995). "Fluctuations in the secretion of pancreatic enzymes between consecutive doses of octreotide: implications for the management of fistulae." European Journal of Gastroenterology & Hepatology **7**(3): 255-8.
- Kusunoki, M., Y. Shoji, et al. (1992). "Treatment of high output enterocutaneous fistulas with a somatostatin analogue and famotidine." European Journal of Surgery **158**(8): 443-5.
- Kwan, D. and A. H. Aufses, Jr. (1989). "Short-term administration of SMS 201-995 in the management of an external pancreatic fistula." American Journal of Gastroenterology **84**(3): 326-8.
- Lansden, F. T., D. B. Adams, et al. (1989). "Treatment of external pancreatic fistulas with somatostatin. Second place winner: Conrad Jobst award." American Surgeon **55**(12): 695-8.
- Mahomed, A. (1997). "Subcutaneously administered somatostatin analogue in traumatic pancreatic fistula [letter]." Pediatric Surgery International **12**(2-3): 231.
- Martineau, P., J. A. Shwed, et al. (1996). "Is octreotide a new hope for enterocutaneous and external pancreatic fistulas closure?" American Journal of Surgery **172**(4): 386-95.
- Nubiola, P., J. M. Badia, et al. (1989). "Treatment of 27 postoperative enterocutaneous fistulas with the long half-life somatostatin analogue SMS 201-995 [published erratum appears in Ann Surg 1990 Feb; 211(2): 246]." Annals of Surgery **210**(1): 56-8.
- Ohta, T., T. Nagakawa, et al. (1992). "Effect of SMS 201-995 on exocrine pancreatic secretion in a patient with external pancreatic fistula." International Journal of Pancreatology **11**(3): 185-9.
- Paran, H., D. Neufeld, et al. (1995). "Preliminary report of a prospective randomized study of octreotide in the treatment of severe acute pancreatitis." Journal of the American College of Surgeons **181**(2): 121-4.
- Poddar, U., R. Kochhar, et al. (1995). "Pancreatico-pleural fistula: successful treatment with octreotide." Indian Journal of Gastroenterology **14**(4): 145-6.
- Ridgeway, M. G. and B. E. Stabile (1996). "Surgical management and treatment of pancreatic fistulas." Surgical Clinics of North America **76**(5): 1159-73.
- Rosenberg, L. and R. A. Brown (1991). "Sandostatin in the management of nonendocrine gastrointestinal and pancreatic disorders: a preliminary study." Canadian Journal of Surgery **34**(3): 223-9.
- Russell, R. C. G. (1996). "Somatostatin in pancreatic disease." British Journal of Surgery December **83**(12): 1665-1667.

- Sargent, A. I., C. C. Overton, et al. (1994). "Octreotide-induced hyperkalemia [see comments]." Pharmacotherapy **14**(4): 497-501.
- Scott, N. A., S. Finnegan, et al. (1990). "Octreotide and gastrointestinal fistulae." Digestion **45**(Suppl 1): 66-70; discussion 70-1.
- Secchi, A., V. Di Carlo, et al. (1992). "Octreotide administration in the treatment of pancreatic fistulae after pancreas transplantation." Transplant International **5**(4): 201-4.
- Segal, I., D. Parekh, et al. (1993). "Treatment of pancreatic ascites and external pancreatic fistulas with a long-acting somatostatin analogue (Sandostatin)." Digestion **54**(Suppl 1): 53-8.
- Shim, K. S., J. M. Suh, et al. (1993). "Three-dimensional demonstration and endoscopic treatment of pancreaticoperitoneal fistula [see comments]." American Journal of Gastroenterology **88**(10): 1775-9.
- Spiliotis, J., D. Briand, et al. (1993). "Treatment of fistulas of the gastrointestinal tract with total parenteral nutrition and octreotide in patients with carcinoma." Surgery, Gynecology & Obstetrics **176**(6): 575-80.
- Tassiopoulos, A. K., G. Baum, et al. (1996). "Small bowel fistulas." Surgical Clinics of North America **76**(5): 1175-81.
- Tulassay, Z., L. Flautner, et al. (1993). "Short report: octreotide in the treatment of external pancreatic fistulas." Alimentary Pharmacology & Therapeutics **7**(3): 323-5.
- Turner, J. W. (1994). "The use of a somatostatin analog in the treatment of an external pancreatic fistula." Missouri Medicine **91**(12): 737-9.
- Vanderkolk, W., D. Scholten, et al. (1996). "Traumatic pancreatic fistula in children - early management with a somatostatin analogue and drainage." Pediatric Surgery International **11**(1): 22-25.
- Wadstrom, J., G. Gannedahl, et al. (1995). "Persistent pancreatic fistula after pancreas transplantation treated with fibrin glue and octreotide." Transplantation Proceedings **27**(6): 3491-2.
- Wallace, A. M. and K. Newman (1991). "Successful closure of intestinal fistulae in an infant using the somatostatin analogue SMS 201-995." Journal of Pediatric Surgery **26**(9): 1097-100.
- Woltering, E. A., T. M. O'Dorisio, et al. (1990). "Treatment of nonendocrine gastrointestinal disorders with octreotide acetate." Metabolism: Clinical & Experimental **39**(9 Suppl 2): 176-9.
- Yeo, C. J. (1994). "Pancreatic pseudocysts, ascites, and fistulas." Current Opinion in General Surgery: 173-8.

Prophylaxis not treatment

- Berberat, P. O., H. Friess, et al. (1999). "The role of octreotide in the prevention of complications following pancreatic resection." Digestion **60**(Suppl 2): 15-22.
- Briceno Delgado, F. J., P. Lopez Cillero, et al. (1998). "[Prospective and randomized study on the usefulness of octreotide in the prevention of complications after cephalic duodeno-pancreatectomy]." Revista Espanola de Enfermedades Digestivas **90**(10): 687-94.
- Buchler, M., H. Friess, et al. (1992). "Role of octreotide in the prevention of postoperative complications following pancreatic resection." American Journal of Surgery **163**(1): 125-30; discussion 130-1.
- Buchler, M. W., H. Friess, et al. (2000). "Pancreatic fistula after pancreatic head resection." British Journal of Surgery July **87**(7): 883-889.
- Delgado, F. J. B., P. L. Cillero, et al. (1995). "Pancreas: A prospective-randomized trial using octreotide in the prevention of postoperative complications following pancreaticoduodenal resection." British Journal of Surgery November **82**(11): 120.

- Delgado, F. J. B., P. L. Cillero, et al. (1998). "A prospective-randomized trial using octreotide for prevention of complications following pancreaticoduodenectomy." Revista Espanola de Enfermedades Digestivas **90**(10): 691-694.
- Friess, H., H. G. Beger, et al. (1995). "Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis." British Journal of Surgery **82**(9): 1270-1273.
- Friess, H. and M. W. Buchler (1996). "Efficacy of somatostatin and its analogues in pancreatic surgery and pancreatic disorders." Digestion **57**(Suppl 1): 97-102.
- Lowy, A. M., J. E. Lee, et al. (1997). "Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease." Annals of Surgery **226**(5): 632-41.
- Montorsi, M., M. Zago, et al. (1995). "Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial." Surgery **117**(1): 26-31.
- Nwariaku, F. E., A. Terracina, et al. (1995). "Is octreotide beneficial following pancreatic injury?" American Journal of Surgery **170**(6): 582-5.
- Paran, H., D. Neufeld, et al. (1995). "Preliminary report of a prospective randomized study of octreotide in the treatment of severe acute pancreatitis." Journal of the American College of Surgeons **181**(2): 121-4.
- Rosenberg, L., P. MacNeil, et al. (1999). "Economic evaluation of the use of octreotide for prevention of complications following pancreatic resection [see comments]." Journal of Gastrointestinal Surgery **3**(3): 225-32.
- Sauvanet, A. and J. Belghiti (1999). "Prevention of pancreatic fistula after Whipple's procedure." Annales de Chirurgie **53**(7): 612-617.
- Yeo, C. J. (1999). "Does prophylactic octreotide benefit patients undergoing elective pancreatic resection? [editorial; comment]." Journal of Gastrointestinal Surgery **3**(3): 223-4.

Non- English

- Briceno Delgado, F. J., P. Lopez Cillero, et al. (1998). "[Prospective and randomized study on the usefulness of octreotide in the prevention of complications after cephalic duodeno-pancreatectomy]." Revista Espanola de Enfermedades Digestivas **90**(10): 687-94.
- Buchler, M., H. Friess, et al. (1990). "[Possibilities of application of octreotide in surgery. 1)Treatment of gastrointestinal fistulas; 2)Prevention of complications in pancreatic surgery]." Zeitschrift fur Gastroenterologie **28**(Suppl 2): 41-4.
- Castanon Gonzalez, J. A., R. Miranda Ruiz, et al. (1992). "[The somatostatin analog SMA (201-995) as adjuvant treatment in patients with external fistulae of the digestive system]." Gaceta Medica de Mexico **128**(3): 285-8.
- Consolo, F. and S. Pustorino (1992). "[Theoretical and physiopharmacological bases of the somatostatin treatment in digestive diseases]." Minerva Chirurgica **47**(8): 723-9.
- Courtin, J. P., M. Di Francia, et al. (1994). "[Efficacy of octreotide acetate in the treatment of a pancreatic-pleural fistula. Apropos of a case]." Revue de Pneumologie Clinique **50**(2): 74-6.
- Engler, S., D. Dorlars, et al. (1996). "[Endoscopic fibrin gluing of a pancreatic duct fistula following acute pancreatitis]." Deutsche Medizinische Wochenschrift **121**(45): 1396-400.
- Feu, F. and J. Bosch (1996). "[Somatostatin and its analogs in the treatment of gastrointestinal and liver diseases]." Gastroenterologia y Hepatologia **19**(2): 68-77.
- Gerardo Perez, D. and M. Bernardo Acosta (1994). "[Gastrointestinal fistulas. Treatment with a somatostatin analogue (SMS 201-995)]." Gen **48**(4): 209-18.

- Hernandez-Aranda, J. C., B. Gallo-Chico, et al. (1996). "[Treatment of enterocutaneous fistula with or without octreotide and parenteral nutrition]." Nutricion Hospitalaria **11**(4): 226-9.
- Karlsborg, M. and B. B. Jorgensen (1992). "[Pancreato-pleural fistula in a patient with chronic pancreatitis]." Ugeskrift for Laeger **154**(5): 275-7.
- Katamura, H., S. Ohki, et al. (1994). "[A case of postoperative cutaneous fistula responding to somatostatin analog, with a special reference to serum level of gastrointestinal hormones]." Nippon Shokakibyo Gakkai Zasshi - Japanese Journal of Gastroenterology **91**(5): 1037-41.
- Leppert, R., K. H. Fuchs, et al. (1996). "[Therapy of upper gastrointestinal fistulas with simultaneous abdominal wall defects]." Zentralblatt fur Chirurgie **121**(Suppl): 82-3.
- Lindsetmo, R. O. and A. Revhaug (1994). "[Treatment of hypersecretory ileostomy, gastrostomy and fistula of the small intestine with the somatostatin analog octreotide]." Tidsskrift for Den Norske Laegeforening **114**(24): 2829-30.
- Lons, T., A. Bruhat, et al. (1991). "[Treatment of pancreatico-pleural fistula with octreotide acetate (letter)]." Presse Medicale **20**(38): 1900.
- Meier, R., R. Dierdorf, et al. (1992). "[Somatostatin analog (octreotide) in clinical use: current and potential indications]." Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine **122**(25): 957-68.
- Munteanu, D., S. Duca, et al. (1998). "[Sandostatin treatment in postoperative external digestive fistulae]." Chirurgia (Bucuresti) **93**(1): 13-21.
- Niv, Y., A. Hadari, et al. (1991). "[Closure of postoperative anastomotic fistulas with a somatostatin analogue]." Harefuah **120**(11): 647-8.
- Paran, H., D. Neufeld, et al. (1991). "[Use of somatostatin analogue for intestinal and pancreatic fistulas]." Harefuah **120**(4): 185-6.
- Saenko, V. F., V. I. Lupal'tsov, et al. (1999). "[The administration of sandostatin in the combined treatment of acute pancreatitis and its complications]." Klinichna Khirurgiia(10): 5-7.
- Serio, G., G. Mangiante, et al. (1995). "[Reoperation in necrotizing acute pancreatitis: evaluation of physiopathology and surgical treatment]." Chirurgia Italiana **47**(2): 43-9.
- Sleth, J. C., Y. Andraos, et al. (1994). "[Value of octreotide in the treatment of postoperative enterocutaneous fistula]." Annales Francaises d Anesthesie et de Reanimation **13**(5): 738-40.
- Stockmann, F. (1991). "[Somatostatin and octreotide in therapy of gastrointestinal diseases]." Zeitschrift fur Gastroenterologie - Verhandlungsband **26**: 166-70.
- Zelli, G. P. (1992). "[Use of octreotide in the treatment of pancreatic fistula]." Minerva Chirurgica **47**(8): 735-6.

APPENDIX

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Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one randomised controlled trials.
Level III	-1	Evidence obtained from pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series (either post-test or pre-test and post-test), descriptive studies, or case studies.

<p>Evidence Summary Therapy</p> <p>Octreotide for enteric and pancreatic fistula</p>	<p>Study 1</p> <p>Sancho JJ, Costanzo J, Nubiola P et al. (1995) Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula. <u>British Journal of Surgery</u> 82:638-41</p>	<p>Study 2</p> <p>Nubiola-Calonge P, Badia JM, Sancho J et al. (1987) Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. <u>The Lancet</u> 2 (8560):672-4</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level II Randomised Controlled Trial</p>	<p>Level II Randomised Controlled Trial</p>
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Patients with postoperative enterocutaneous fistula Intervention: Octreotide 100 µg in 1ml 0.9% saline by subcutaneous injection every 8 hours. Comparison: Placebo (saline alone) Outcomes: Fistula output, rate of closure Incl & Excl Criteria: Included if fistula was of stomach of small bowel origin, less than 8 days in duration, and output greater than 50 ml. Excluded if fistula arose from neoplastic or irradiated tissues, gross anatomical abdominal wall defects, mucocutaneous continuity, or colonic anatomised.</p>	<p>Patients: Patients with postoperative small-bowel fistulae. Age 23 to 71 years (mean 54). Intervention: Octreotide for two days (dosage 0.225-0.300 mg per 24 hours given subcutaneously every 8 hours) and then placebo for another two days. Comparison: Placebo for two days and then octreotide for another two days (dosage 0.225-0.300 mg per 24 hours given subcutaneously every 8 hours) . Outcome: Fistula output Incl & Excl Criteria: Included if persistent fistulous drainage for at least 7 days before the study while on parenteral nutrition, fistula not originating in cancerous or necrotic/ischaemic bowel, and growth finished.</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: By drawing of consecutively numbered drug packages that contained either treatment. All patients accounted for: Yes Patients treated equally: Yes Similar groups: Yes for demography, fistula origin and severity, and nutritional and septic status. Potential for bias: Low potential for bias</p>	<p>Randomisation: Yes, method not specified. All patients accounted for: Yes Patients treated equally: Yes Similar groups: There is no data or analysis provided of group characteristics. Potential for bias: Unclear randomisation, potentially small sample size, potential washover effects due to cross over of intervention and placebo.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>There were no differences in mean reduction of output compared with pre-treatment values between patients given octreotide and placebo at 24 hours (66% vs. 68%, p=0.9), 48 hours (60% vs. 57%, p=0.8), and 72 hours (62% vs. 66%, p=0.9). Mean time to closure was not significantly less in patients receiving octreotide than in those given placebo (7% vs. 12%, p=0.16). Closure within 20 days was observed in 8 of 14 fistulas inpatients given octreotide and in six of 17 patients receiving placebo (p=0.4). There were no major adverse effects. There were two deaths in each group.</p>	<p>Octreotide reduced fistula output in all patients. In the placebo-octreotide group fistula output was reduced significantly (from a mean of 828 ml per 24 hours on day 2 on placebo to 247 ml per 24 hours on day 1 on octreotide, p<0.01). Placebo had no effect. An increase was seen when treatment with octreotide was interrupted by placebo (228 ml per 24 hours vs. 498 ml pe3r 24 hours, p=0.014).</p>
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>"Administration of octreotide, within 8 days of fistula onset, associated with parenteral nutrition does not significantly increase the spontaneous fistula closure rate compared with parenteral nutrition plus placebo."</p>	<p>"We conclude that octreotide seems to be safe and that it significantly reduces enterocutaneous fistulae output and accelerates their spontaneous closure, thereby reducing the period of parenteral nutrition and time in hospital. It can thus diminish the morbidity inherent to long lasting conservative treatment."</p>

<p>Evidence Summary Therapy</p> <p>Octreotide for enteric and pancreatic fistula</p>	<p>Study 1 (cont...)</p> <p>Sancho JJ, Costanzo J, Nubiola P et al. (1995) Randomized double-blind placebo-controlled trial of early octreotide in patients with postoperative enterocutaneous fistula. <u>British Journal of Surgery</u> 82:638-41</p>	<p>Study 2 (cont...)</p> <p>Nubiola-Calonge P, Badia JM, Sancho J et al. (1987) Blind evaluation of the effect of octreotide (SMS 201-995), a somatostatin analogue, on small-bowel fistula output. <u>The Lancet</u> 2 (8560):672-4</p>
<p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p>	<p><u>Strengths</u></p> <ul style="list-style-type: none"> • Sample size calculation was performed prior to commencement of the trial • Groups were similar at the commencement of the trial • Groups were treated equally except for the intervention • Patients and staff were blinded to group allocation <p><u>Weaknesses</u></p> <ul style="list-style-type: none"> • Power calculation determined that 15 patients would be required in each group but only 14 were allocated to the octreotide group 	<p><u>Strengths</u></p> <ul style="list-style-type: none"> • Clear inclusion/exclusion criteria • Groups were treated equally • Treatment sequence was blindly allocated <p><u>Weaknesses</u></p> <ul style="list-style-type: none"> • We are unclear if groups were truly randomised • No sample size (power) calculation was performed to determine the number of subjects need to detect a difference between the groups • There may be residual effect after the cross over period. The length of time spent in each cross over arm may not have been appropriate. • The groups may not have been similar/ comparable at the start of the trial • Only one outcome was measured

<p>Evidence Summary Therapy</p> <p>Octreotide for enteric and pancreatic fistula</p>	<p>Study 3</p> <p>Scott NA, Finnegan S, Irving MH. (1993) Octreotide and postoperative enterocutaneous fistulae: a controlled prospective study. <i>Acta Gastroenterologica Belgica</i> 56(3-4):266-70</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level II Randomised Controlled Trial</p>
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Patients with postoperative enterocutaneous fistulae Intervention: Subcutaneous octreotide injections (100µg tds) Comparison: Subcutaneous placebo injections (acetate buffered saline) Outcomes: Fistula output Incl & Excl Criteria: Included if gastric, duodenal, pancreatic or small bowel fistula, no abscesses, and no distal obstructions. Excluded if complete discontinuity, foreign bodies, spontaneous fistulating (Chrons, malignancy, radiation enteritis), mucosal-skin continuity, or epithelialised tracks.</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: Yes, method not specified All patients accounted for: Yes, although there was a high drop out rate Patients treated equally: Yes Similar groups: Yes for fistula output during baseline period. There were more males in the octreotide group and patients were older in the placebo group. There were more small bowel fistulas in the octreotide group and more duodenal fistulas in the placebo group. These differences were not tested statistically Potential for bias: High drop out rate, no power (sample size) calculations. Groups differed at commencement of trial.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>There were no statistically significant differences between the octreotide and placebo groups in fistula output for 12 days following treatment.</p>
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>"In a double blind prospective study of 19 patients with enterocutaneous fistulae, octreotide therapy was neither associated with a significant reduction in fistula losses nor an increased rate of spontaneous fistula closure."</p>
<p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p>	<p><u>Strengths:</u></p> <ul style="list-style-type: none"> • Trial was randomised • Both subjects and clinicians were blinded to group allocation • The groups were treated equally with both groups receiving treatment in the form of a subcutaneous injection • Clear inclusion/ exclusion criteria <p><u>Weaknesses:</u></p> <ul style="list-style-type: none"> • Study had a high drop out rate, with a high proportion of patients not being included in the evaluation • Small sample size. Study probably did not have sufficient power to detect a difference between groups • The groups did differ in demographic characteristics at the start of the trial