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Title	South Australian experience with paediatric total pancreatectomy and islet autotransplantation for *PRSS1*-associated hereditary pancreatitis

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/MJA2.51247

	Institution		City	State		
1	Women's and Children's Hospital		Adelaide	SA		
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3	Flinders Medical Centre		Adelaide	SA		
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Primary Keywords [Office use only]	Surgical procedures, operative; Digestive system diseases; Pediatric medicine
Secondary keywords [Office use only]	Transplantation; Pancreas transplantation; Pancreatic diseases; Childhood diseases
Notes:	

Article details (press ctrl – 9 to enter details):

Article type	Perspective
Blurb	Evidence supports the establishment of a national TP-IAT program, delivered at sites with a concentration of expertise and experience

Office use

Ms. Number	mja20.01386.R3
Medical editor	Tania (Tatiana) Janusic
Medical editor email	tjanusic@mja.com.au
Structural editor	Graeme Prince
Structural editor email	gprince@mja.com.au
Section/Category	Perspective (2-pp)
Strapheading	Perspective
Substrap	

Wiley – file data:

Filename for copyediting	eld_mja20.01386_ms
Accompanying graphics	
Stock images	
Appendices	

Office use – history:

Event	Date
Original submission received	17/12/2020

Event	Date
Accept	17/06/2021

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	04/10/21
Issue	7
Vol	215
DOI	10.5694/mja20.01386
Journal	The Medical Journal of Australia
Original article DOI (for response)	

South Australian experience with paediatric total pancreatectomy and islet autotransplantation for *PRSS1*-associated hereditary pancreatitis

Evidence supports the establishment of a national TP-IAT program, delivered at sites with a concentration of expertise and experience

Chronic pancreatitis is probably an underestimated cause of chronic abdominal pain in children, and its true incidence remains unknown.[1] Chronic inflammatory cell infiltration and fibrosis of pancreatic tissue results in exocrine and endocrine insufficiency with malabsorption and ultimately diabetes mellitus. Although obstruction, toxins and other factors can be associated, genetic mutations contribute toward childhood chronic pancreatitis in 65–75% of cases.[2,3]

By far the most common genetic mutation involves the cationic trypsinogen gene *PRSS1* (serine protease type 1). These mutations cause failure of acinar cell feedback mechanisms, enhancing activation or preventing inactivation of acinar cationic trypsinogen production.[4] This results in pancreatic autodigestion, inflammation and/or fibrosis.[4] *PRSS1* mutations have a high penetrance, with clinical sequalae in more than 90% of cases.[3] Resulting chronic pancreatitis is associated with a lifetime pancreatic cancer risk in excess of 40%.[5] Gain of function mutations N29I and R122H are the most common *PRSS1* mutations, and these exhibit more severe disease progression.[3] Other mutations predisposing chronic pancreatitis include pancreatic sufficient mutations in the cystic fibrosis transmembrane regulator gene, and mutations in the serine peptidase inhibitor Kazal type 1 and chymotrypsin C genes.[2,3] Calcium-sensing receptor, carboxypeptidase 1, claudin 2, carboxyl ester lipase and carboxyl ester lipase hybrid gene mutations have also been reported.[3]

Paediatric chronic pancreatitis can significantly reduce quality of life with frequent hospitalisation, school absence and disrupted daily activities.[2,5-7] One-third of affected children require opioids to manage pain symptoms.[7] Pancreatic enzyme replacement is often used to reduce pancreatic stimulation. Endoscopic interventions including duct

decompression via endoluminal dilatation, stenting, stone retrieval or sphincterotomy may be helpful in managing severe disease.[5,6] Traditionally, surgical interventions have included limited resection or drainage of a diseased gland, including Whipple or Puestow procedures.[2,7] Total pancreatectomy and islet autotransplantation (TP-IAT) has emerged as the therapy of choice for disabling, acute recurrent or chronic pancreatitis refractory to medical and endoscopic therapies.[8]

The first TP-IAT undertaken in a child was described in 1996.[9] TP-IAT is now known to improve quality of life in paediatric patients with severe chronic pancreatitis.[5-7] This complex, life-transforming procedure requires surgical, laboratory and interventional radiological expertise. Early referral for TP-IAT in affected children should be considered, noting that previous surgical intervention can negatively impact islet yield and increase post-operative infection.[5-7]

Funding for islet transplantation in Australia is currently provided solely for hypoglycaemic unawareness complicating type 1 diabetes.[10] Islet allotransplantation carries risks associated with obligate immunosuppression and rejection that are not seen with autologous islet transplant.[11] A collaborative initiative has attracted philanthropic funding of a paediatric TP-IAT program at the Women's and Children's Hospital in Adelaide, South Australia, in consultation with overseas expertise. This staged procedure was achieved with same-day islet isolation and preparation at the St Vincent's Institute of Medical Research in Melbourne. We report our experience with five children who underwent TP-IAT in this program. All patients had hereditary pancreatitis caused by a mutation in the *PRSS1* cationic trypsinogen gene. Pre-operative, intra-operative and post-operative care is described in the Supporting Information.

Characteristics of our cohort are listed in the Box. Age at time of TP-IAT ranged from 7.9 to 17.8 years. Four children were female. Three were of Aboriginal and Torres Strait Islander background. Each child fulfilled published University of Minnesota criteria for TP-IAT and recommendations from PancreasFest in 2014.[5,12] Three had N29I mutations and two had R122H mutations in the *PRSS1* gene. Frequent admissions (median, 13.5 pre-operatively), chronic symptoms and narcotic requirements impacted school attendance and quality of life. Two patients had required previous stenting and/or sphincterotomy, and one had undergone a Puestow (cyst jejunostomy) procedure. All were prescribed pancreatic enzyme replacement to reduce pancreatic stimulation.

Younger age is a favourable prognostic factor for achieving insulin independence following TP-IAT.[5] Larger paediatric series have shown more than 60% are insulin independent or require minimal exogenous insulin at 1 year,[5] with rates as high as 80% in children aged 3–8 years.[7] Overall, insulin independence has been seen in up to 40% of paediatric patients at 10 years after TP-IAT.[4]

Yields of more than 2500 islet cell equivalents per kilogram of body weight (IEQ/kg) during intra-operative islet laboratory preparation correlate with better outcomes.[6,7] In an adult case series, more than two-thirds of patients achieved insulin independence at 3 years with an IEQ/kg > 5000, up to one-fifth with an IEQ/kg of 2500–5000, and 12% in

those with an IEQ/kg < 2500.[8]

Four of five children in our cohort had excellent islet yield, ranging from 7299 to 11 665 IEQ/kg (Box). Follow-up revealed long term insulin independence in two of these patients, with encouraging progress in a third patient who now has negligible requirements and a normal glycated haemoglobin level of 5.5%. The fourth patient became insulin independent 8 months post-operatively, but developed an insulin requirement associated with glutamic acid decarboxylase islet antibodies 20 months later. The patient with the lowest islet yield (IEQ/kg, 1130) had a long term insulin dependence. This was reflected early via delay in detecting C-peptide post-operatively, and advanced pre-morbid disease with extensive atrophy and calcification of pancreatic tissue on imaging (Box). Despite this, following TP-IAT, the child no longer required opiates, had enhanced growth, and re-engaged in normal childhood activities including competitive sport.

Internationally, TP-IAT is associated with improved scores on health-related quality of life questionnaires, including school attendance and reduced opioid requirements.[6,7] This remained true regardless of ongoing insulin dependence.[6] Narcotic independence in children following TP-IAT is seen in 50–80% at 1 year,[5,7] with higher success in younger children aged under 8 years.[7] Although formal quality of life assessments were not pursued in our cohort, all became independent of opioids. All resumed normal activities, including schooling and sport, with restoration of daily function regardless of ongoing insulin requirements. All of the families and patients have been pleased with the outcome.

Five of the seven paediatric TP-IAT procedures performed in Australian children by May 2021 have been undertaken in Adelaide, as part of a multicentre collaborative effort. Interstate transport for remote islet cell isolation has not proven an impediment to the procedure or its outcome, as demonstrated by other groups.[13,14] We plan to perform laboratory islet isolation locally in the future. In our cohort of children with a substantial morbidity from *PRSS1* pancreatitis and a high pancreatic cancer lifetime risk, we have achieved marked improvement in quality of life irrespective of the potential burden of long term insulin requirements. Children with higher IEQ/kg appeared to have a greater chance of achieving and maintaining insulin independence.

We believe this procedure is of great benefit to Australian children with a significant burden of disease from chronic pancreatitis, which may be generally under-recognised. However, this complex undertaking relies on considered patient selection, involvement of multiple specialists and meticulous planning to orchestrate staged theatre and high dependency care. For biliary atresia, British paediatric surgeons have proposed that Kasai hepatoportoenterostomy be performed at selected centres.[15] The case for TP-IAT, a similarly complex two-stage procedure, to be undertaken at sites with appropriate expertise and experience as part of a national initiative is compelling.

Acknowledgements: We thank Paul Flynn and the Hospital Research Foundation in South Australia, who enabled funding of four of five TP-IAT procedures undertaken, along with the attendance of international experts to help with the islet isolation process. We also thank Melena Bellin (University of Minnesota), Ashley Dennison (University of Leicester), Greg Szot (University of California, San Francisco) and Appakalai Balamurugan (University of Louisville)

for their contributing expertise. We also acknowledge the clinicians involved in the patients' care during and following the procedures, including from the islet transplant and interventional radiology services at the Royal Adelaide Hospital; the gastroenterology, endocrinology and paediatric intensive care units at the Women's and Children's Hospital, Adelaide; and the islet transplantation laboratory at St Vincent's Institute of Medical Research, Melbourne.

Competing interests: Toby Coates has received grants and funding from Kidney Transplant Diabetes Research Australia.

Provenance: Not commissioned; externally peer reviewed.

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doi: 10.5694/mja20.01386

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[Box]

Patient characteristics and operative outcomes in children who underwent total pancreatectomy and islet autotransplantation (TP-IAT) at the Women's and Children's Hospital, Adelaide (*n* = 5)

	Median (IQR)	Number of patients
Patient characteristics		
Age at time of TP-IAT (years)	16.8 (8.1–17.8)	
Number of pancreatitis hospital admissions prior to TP-IAT	13.5 (11.5–20.0)	
PRSS1 mutation		
N29I		3
R122H		2
Sex		
Male		1
Female		4
Pre-operative imaging changes		
Pancreatic duct dilatation		4
Pancreatic calcification		2
Major atrophy of pancreatic tissue		2
Previous operations/relevant procedures		
ERCP-based interventions (including dilation, stenting, sphincterotomy)		2
Cyst jejunostomy (Puestow procedure)		1
Operative outcomes		
Minutes from pancreatectomy to laboratory enzyme perfusion (minutes)	300 (268–344)	
Time from pancreatectomy to islet cell infusion (hours)	13 (11–13)	
IEQ	489 000 (165 356–605 129)	
IEQ/kg	8192 (4215–11 561)	
Transition from insulin infusion to subcutaneous insulin pump following TP-IAT (days)	12.0 (12.0–13.5)	
Paediatric ICU duration (days)	7.0 (6.5–12.0)	
Length of stay in hospital (days)	30.0 (17.5–30.5)	
Post-operative complications		
Suspected portal vein thrombosis		1
Bleeding pyloroanastomotic ulcer		1
Splenic vein bleed (requiring repeat laparotomy)		1

Bacterial growth islet cell culture	2*,†
Small bowel obstruction secondary to internal hernia	1
Post-operative dysmotility/gastroparesis	2
Presumed cholangitis	1†
Long term insulin requirements	
Insulin independent	2
Insulin requirement ongoing	3‡
Long term opioid requirement	0

ERCP = endoscopic retrograde cholangiopancreatography; ICU = intensive care unit; IEQ = islet cell equivalents (equating to an islet size of 150 μm diameter); IEQ/kg, IEQ per recipient kilogram of weight; IQR = interquartile range. * *Graniculatella* in one patient. † *Escherichia coli* in one patient (note: previous Puestow procedure in this patient). ‡ One patient was initially insulin independent but developed glutamic acid decarboxylase islet antibody-positive type 1 diabetes 20 months post-operatively; one patient had weaning requirements post-operatively.