出國報告(出國類別：進修)

美國加州大學舊金山分校附設醫院移植外科臨床進修胰臟移植回國報告

服務機關：國防醫學院三軍總醫院
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派赴國家：美國
報告日期：103 年 1 月 6 日
出國時間：102 年 6 月 29 日至 103 年 1 月 1 日

摘要

於102年6月29日至12月31日至美國加州大學舊金山分校附屬醫院移植外科接受六個月的胰臟移植進修，我的指導教授是Sandy Feng教授，進修期間學習到胰臟移植的手術經驗，也參與了手術前評估及手術後的住院及門診照顧。在手術後的住院照顧，觀察到手術後併發症的處理方式，也包含了術後排斥的治療方法。

胰臟移植手術能否順利的執行有賴於移植團隊對捐贈者狀況的判斷、手術醫師的經驗技術、受贈者的術前評估及手術後團隊的照顧等，其中又以移植團隊中各醫護人員之間的合作溝通最為重要，才能順利完成手術並提供高品質的醫療照顧。

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壹、目的

本院目前已經建立心臟、肝臟、腎臟及眼角膜移植之制度，但至今仍未建立胰臟移植之制度，而本院為一醫學中心，負有提供全方位的醫療服務及提升醫療品質之任務，需建立一套完整的胰臟移植之制度，提供軍人、軍眷及民眾最優質的醫療服務。

貳、過程

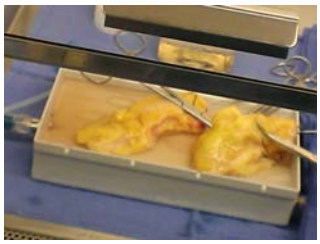
102 年 6 月 29 日抵達美國舊金山後，利用兩天安頓好生活起居後，於 7 月 1 日開始我的進修生活。我的指導教授是 Sandy Feng 教授，加州大學舊金山分校 University of California, San Francisco (UCSF)移植外科的進修計劃主持人，對於移植手術及移植免疫有傑出的研究成果。而 UCSF 是目前在美國移植手術存活率高於平均值的醫學中心之一，且從 2003 年至 2012 年共施行 258 例胰臟移植手術，所以來到這裡進修學習移植手術技巧、手術前評估及手術後照顧，覺得有很大的收穫，也深感在進修回國後才能提供病人優良的醫療照顧。以下就先介紹我進修過程中每週的行程：

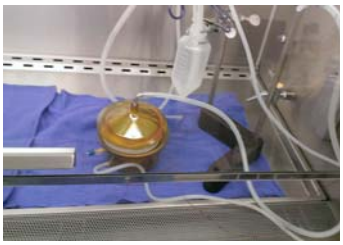
- ☆ 每日參與巡房教學
- ☆ 每週二、三參與門診教學
- ☆ 每週二、四參與手術教學
- ☆ 每週一參與器官移植術前評估會
- ☆ 每週三參與 Surgical Grand Round
- ☆ 每週五參與死亡及併發症討論會
- ☆ 不定期參與器官摘取手術

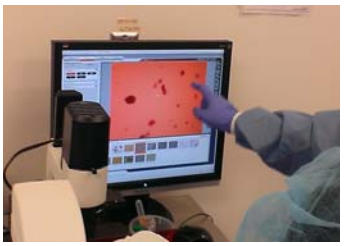
另外，我在 102 年 8 月 6 日第一次參加了胰島細胞萃取的實驗，而 UCSF 的胰島細胞萃取實驗室，是少數獲得 GMP 認證標準的實驗室。

在 102 年 9 月 24 日至 9 月 27 日參加了國際胰臟及胰島移植學會(IPITA)在加州蒙特雷所舉辦的年會，得知世界各國目前對於胰臟及胰島移植的最新資訊及未來發展方向。

在 102 年 10 月 16 日參與胰臟全切除及胰島自體移植的手術，病人的血糖在胰島細胞移植注射進入肝門靜脈後，很快就控制下來到正常值，表示自體移植的胰島細胞開始作用產生胰島素來控制血糖。







參、心得

胰臟器官的捐贈

因為 UCSF 並沒有進行活體胰臟移植手術，所以胰臟器官的捐贈都來自腦死的病人，而胰臟捐贈者的選擇條件比肝臟及腎臟器官捐贈者來的嚴格。

Table 10.1 Pancreas donor criteria.

Ideal pancreas donor	
Young age	8–45 years
Normal body habitus	BMI 20–27
ICU stay	Short period of ICU stay
Cause of death	Brainstem death following head injury
Hemodynamic stability	Minimal use of inotropes
Acceptable donor criteria	
Age	8–60 years
BMI	<30 kg/m²

理想的胰臟捐贈者為：

- 年齡： 8~45 歲
- 身體質量比 BMI 介於 20~27
- 加護中心短期滯留
- 死亡原因：單純因腦外傷而腦死
- 生命徵象穩定：使用少量的升壓藥物

可接受的胰臟捐贈者為：

- 年齡： 8~60 歲
- 身體質量比 BMI 小於 30

另外，在檢視捐贈者的病歷時，要注意捐贈者是否有胰島素依賴(insulin dependence)的情形，個人病史需注意是否有胰臟炎、喝酒及抽煙的病史。

當然在器官摘取手術前需要檢查捐贈者與受贈者的：

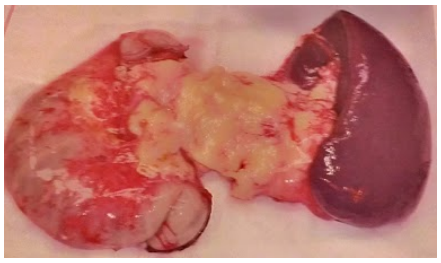
- 血型配對(ABO matching)
- 人類白血球抗原配對(HLA typing)
- 抗體篩選(PRA: panel reactive antibody)
- 淋巴球毒性交叉配對

而胰臟移植需要合適的血型配對及淋巴球毒性交叉配對為陰性才能進行手術。

捐贈者手術

腹腔打開後，在取完肝臟後，接下來便輪到胰臟之摘取，摘取前需先檢視胰臟之外觀，若有下列之情形，則胰臟不適合進行移植：

- ☆ 胰臟外觀包膜之損傷
- ☆ 胰臟實質之裂傷
- ☆ 胰臟血腫
- ☆ 胰臟血管之損傷
- ☆ 胰臟脂肪浸潤嚴重
- ☆ 胰臟纖維化嚴重



不適合進行移植之胰臟(圖片摘錄於 Atlas of organ transplantation)

將鼻胃管放入十二指腸中，使用約 500ml 的 amphotericin solution(50mg/L)或是 iodine soultion 清洗十二指腸，接著將 Gastrocolic ligament 完全分開，以便完整看到胰臟，接著將脾臟週邊的 ligament 完全分開，將脾臟提起後，便可將胰臟的尾部及體部自後腹腔分離。將十二指腸第一部分分離後，用自動縫合器在幽門遠端將十二指腸與幽門截斷，同樣地，用自動縫合器在 Treitz ligament 遠端將十二指腸與空腸截斷。由於肝臟摘取小組會將脾動

脈從腹腔幹動脈(Celia trunk artery)的源頭處截斷，可用 6/0 prolene 縫在脾動脈斷端處來標記，以便於作動脈血管重建；另外，需協調肝臟摘取小組保留至少 10mm 長度的肝門靜脈於胰臟端，以便於作靜脈血管重建；上腸系膜動脈(Superior mesenteric artery, SMA)可以在腹主動脈出口處截斷(需注意不要傷害到腎動脈)，胰臟摘取下來後，需要在 20 小時內移植，否則會明顯增加手術後的併發症。

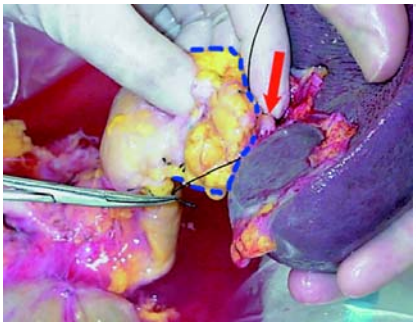
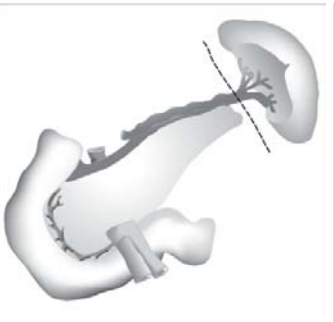
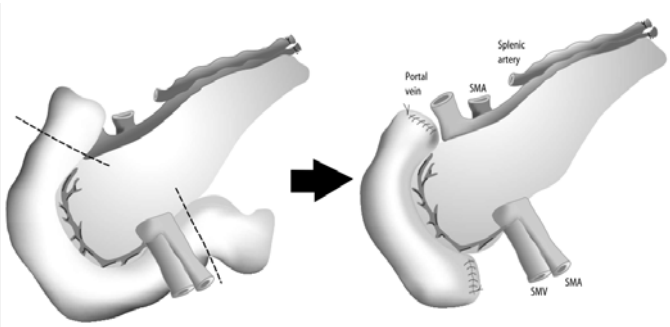
後桌手術(Back table operation)

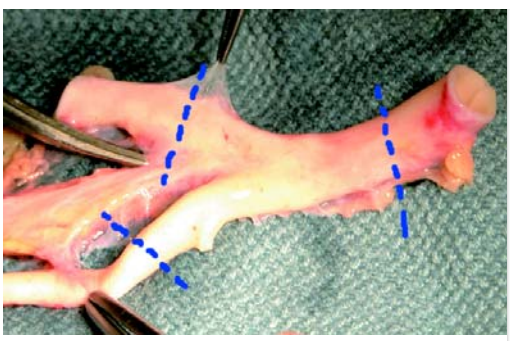
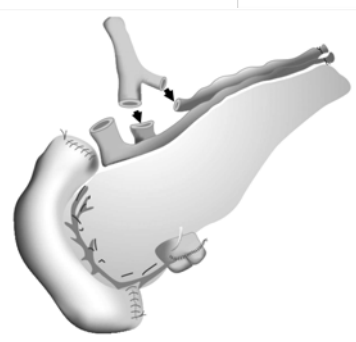
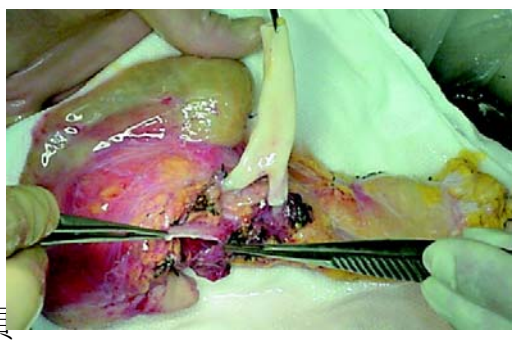
手術開始前還是需要先觀察胰臟是否有任何損傷及脂肪浸潤情形，確定外觀沒問題後再進行手術，手術進行時也要小心處理器官，不要造成其他額外的損傷。以下是Back table operation的基本原則：

- ☆ 切除脾臟
- ☆ 切除胰臟週邊多餘的組織及脂肪 (殘留多餘的組織及脂肪將導致術後感染)
- ☆ 將脾動脈、上腸系膜動脈、肝門靜脈分離出來並切除週邊多餘的組織
- ☆ 切除多餘的十二指腸
- ☆ 用 Y graft(將從捐贈者取下來的髂動脈)連接脾動脈及上腸系膜動脈

脾臟切除時需在靠近脾門(splenic hilum)處截斷脾動靜脈，小心避免傷害到胰臟尾部，在切除胰臟週邊多餘的組織及脂肪時，需要適當的結紮以避免血流灌注回溫時出血，在胰臟上方清除多餘組織時，小心避免傷害到脾動脈，同樣地，在分離脾動脈、上腸系膜動脈及肝門靜脈時，要小心避免傷害到血管，也不要傷害到胰臟的表面，另外，需要檢視總膽管已經適當的結紮，避免術後膽汁滲漏；在胰臟下方清除多餘組織後，仔細將上腸系膜動脈及靜脈從腸系膜出口處縫合結紮。將十二指腸留下第二部分，其餘部分與胰臟分離後用自動縫合器切斷分離；利用 Y graft 準備做動脈重建，將上腸系膜動脈與脾動脈修剪適當長度後與 Y graft 用 6-o Prolene 做血管吻合(end to end anastomosis)，需避免吻合後造成血管翻轉或是過長，以免手術後血管產生血栓而阻塞。

(圖片摘錄於 Atlas of organ transplantation)

受贈者手術

如果胰臟與腎臟同時移植，胰臟移植手術的基本原則如下：

☆ 胰臟優先移植至右下腹，腎臟之後移植至左下腹

☆ 將右側大腸分離推至左側以呈現出右側總髂骨動靜脈

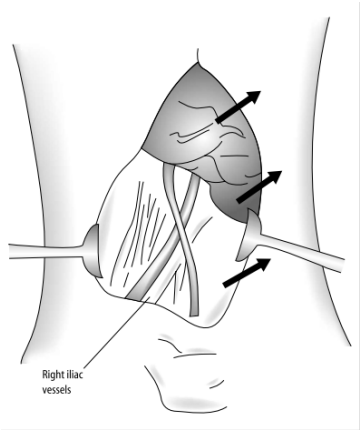
☆ 將右側總髁骨動脈及靜脈分離出來並結紮週邊多餘的分支

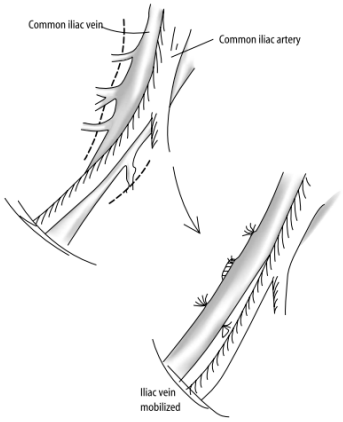
☆ 完成動脈及靜脈之吻合(4-stitch technique)

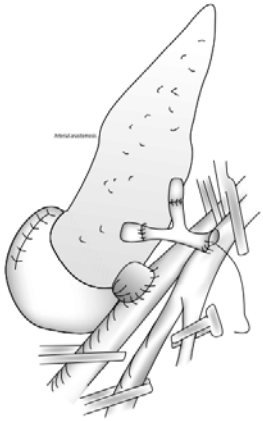
☆ 血液灌注回溫後，仔細結紮出血點並檢查胰臟及十二指腸是否有缺血之情形

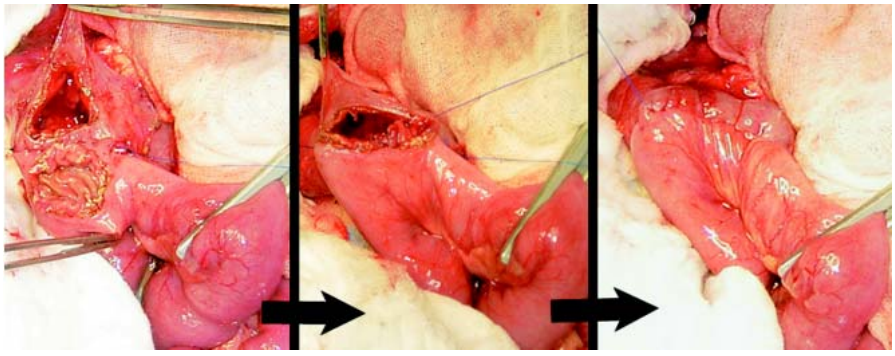
☆ 完成捐贈者十二指腸與受贈者小腸吻合(side to side anastomosis)

病人以平躺姿勢，經下腹中線的切口打開腹腔後，將右側大腸分離後，用 Codman retractor 將右側大腸推至左側以呈現出右側總髂骨動脈及靜脈，將右側總髁骨動脈及靜脈分離出來並結紮週邊多餘的分支同時檢查是否有動脈粥狀硬化的情形，用碎冰浸泡的紗布包裹胰臟尾端，擺放至適當角度準備做血管吻合，用血管夾夾住血管吻合處之上下端後，用 5-0 Prolene 先做靜脈吻合，再用 6-0 Prolene 做動脈吻合，在血液灌注回溫前，需先使用 Heparin 以預防血栓產生，回溫後，仔細結紮出血點並檢查胰臟及十二指腸是否有缺血之情形，最後將捐贈者十二指腸與受贈者小腸做腸吻合(side to side anastomosis)，同時收集十二指腸液體培養，以作為術後抗生素使用之依據，而後放置引流管並縫合腹腔完成手術。









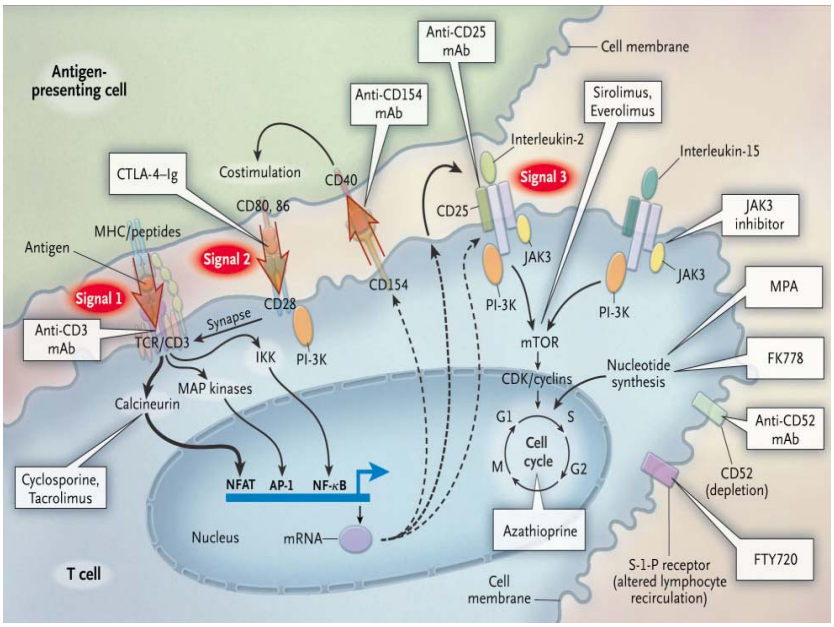
(圖片摘錄於 Atlas of organ transplantation)

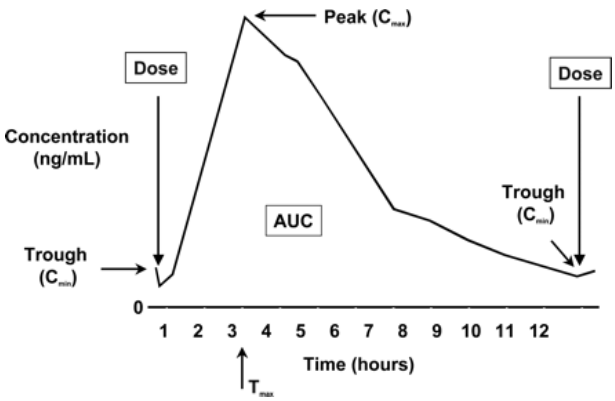
免疫藥物

在 UCSF 的治療準則中免疫誘導(Induction)是採用 Steroid and Thymoglobulin，免疫維持(Maintenance)是採用 Steroid、MMF、Tacrolimus and Sirolimus，治療劑量及時間如下表：

Steroid avoidance protocol	Steroid use protocol
For: unsensitized SPK PAK if not already on steroids To monitors rejection, PAK recipients will have regular protocol biopsies at 3 months	For: high risk patients(2^{nd} transplsant, high PRA) PTA PAK already on steroids To monitors rejection, PTA/PAK recipients will have regular protocol biopsies at 3 months
INDUCTION **Solumedrol** In OR: 500mg immediately following initial abdominal exploration POD#1: 250mg POD#2: 2mg/kg POD#3~4: 0.5mg/kg POD#5: no further solumedrol unless patient is in ATN, is still receiving Thymo, or has inadequate levels of tacolimus. Dose is 0.5mg/kg	INDUCTION **Solumedrol** In OR: 500mg immediately following initial abdominal exploration POD#1: 250mg POD#2: 2mg/kg POD#3 and until Thymo done: 0.5mg/kg POD#7: decrease by 10mg/week until 20mg then taper weekly – 15mg,12.5mg, 10mg, 7.5mg, stop at 5mg
Thymoglobulin In OR: 1.5mg/kg (rounded to nearest 25mg), started 30 min after Solumedrol and infused over 6 hrs with pump POD#1: 1mg/kg. Continuous QD until 6mg/kg has been given. If ATN: attempt to continuous Thymo QOD until calcineurin inhibitors can be started. Always given after Steroids. ＊Adjust dose for WBC and Platelet counts ＊First 48 hours of Thymo therapy: Acetaminophen 650mg PR Q 4 hrs Diphenhydramine 25~50mg po/IV Q 6hrs	**Thymoglobulin** In OR: 1.5mg/kg (rounded to nearest 25mg), started 30 min after Solumedrol and infused over 6 hrs with pump POD#1: 1mg/kg. Continuous QD until 6mg/kg has been given. If ATN: attempt to continuous Thymo QOD until calcineurin inhibitors can be started. Always given after Steroids. ＊Adjust dose for WBC and Platelet counts ＊First 48 hours of Thymo therapy: Acetaminophen 650mg PR Q 4 hrs Diphenhydramine 25~50mg po/IV Q 6hrs

MAINTENANCE Tacrolimus (Prograft) Start when evidence of good renal function Give NG or PO: very few indications for IV administration If pt already on Tacrolimus and has poor oral intake, IV dose should not exceed 1mg over 24 hrs as a continuous infusion. (Total dose of 1mg over 24 hrs) Start levels after two doses given. Run QD except Sun. Adjust doses keeping in mind renal function and drugs metabolized by Cytochrome P450, such as fluconazole Target levels: 0~3 months: 15 ng/ml 3~6 months: 10 ng/ml > 6 months: 5 ng/ml	MAINTENANCE Tacrolimus (Prograft) Start when evidence of good renal function Give NG or PO: very few indications for IV administration If pt already on Tacrolimus and has poor oral intake, IV dose should not exceed 1mg over 24 hrs as a continuous infusion. (Total dose of 1mg over 24 hrs) Start levels after two doses given. Run QD except Sun. Adjust doses keeping in mind renal function and drugs metabolized by Cytochrome P450, such as fluconazole Target levels: 0~3 months: 15 ng/ml 3~6 months: 10 ng/ml 6 months: 5 ng/ml The lowest level, or "trough" blood level: must wait to take your morning dose of medication until after the blood level has been drawn
Myfortic Pre-op: 720mg po with sip of water Starting POD#1: 360mg po BID, increase to 720mg after Thymo ends and until Rapamune starts, then drop to 360mg BID Taper for leucopenia or GI irritation DC Cellcept at 6 months	Myfortic Pre-op: 720mg po with sip of water Starting POD#1 and while on Thymo: 360mg po BID When Thymo done: 720mg po BID Reduce to 360mg bid when Rapamune starts Taper for leucopenia or GI irritation Consider DC after 1 year
Sirolimus (Rapamune) Start at 3 weeks, 3mg po QD, No loading dose Sirolimus level before 4th dose and Q week Target level: 10 ng/ml Adjust dose for leucopenia or thrombocytopenia	Sirolimus (Rapamune) Start at 3 weeks, 3mg po QD, No loading dose Sirolimus level before 4th dose and Q week Target level: 10 ng/ml Adjust dose for leucopenia or thrombocytopenia





其他藥物

ANTICOAGULATION

Simultaneous Pancreas-Kidney transplant (SPK)

Pre-op: ASA 325mg po x 1

Dipyridamole 200mg po x 1

POD#1: ASA 325mg po x 2 weeks or indefinitely if no contraindication

Dipyridamole 75mg po qid x 2 weeks

Solitary Pancreas Transplants (PTA/PAK)

Pre-op: ASA 325mg po x 1

No Dipyridamole (Persantin)

Full heparinization at time of clamping

CBC and Coagulation test checked q4h post-op, low dose heparin infusion started 6 hours and continued x 3 days (After first 24 hours, CBC and Coagulation test checked q6h)

POD#1: ASA 325mg po x 2 weeks or indefinitely if no contraindication

Dipyridamole 75mg po qid x 2 weeks. Start after heparin discontinued.

ANTIBIOTIC PROPHYLAXIS

Early post-op broad-spectrum coverage

Zosyn adjust for renal function

(Alternate therapy if patient allergic to above drugs: Levofloxacin 500mg iv q24h)

Continue for 5 post-op days, then DC if donor duodenal cultures negative.

If donor duodenal cultures positive for bacterial pathogens, change antibiotic as needed and continue for a total of 10 post-op days

Fungal prophylaxis

Pre-op: Fluconazole 400mg iv x1

POD#1~5: Fluconazole 200mg iv qd

After POD#5: Fluconazole 100mg po q week x 2 months if donor duodenal cultures negative
Fluconazole 200mg po qd x 1 month if donor duodenal cultures positive for fungal pathogens, then 100mg po q week x another month.

Watch Prograf levels when transition off daily Fluconazole (使用較高劑量 Fluconazole 會導致 Prograf level 升高，應降低 Prograf dose)

PCP prophylaxis

Septra DS po qd x 1 month, then q M-W-F (W1,3,5) indefinitely

If allergic to Septra: check G6PD (If not low) start Dapsone 100mg po qd x 1 month, then q M-W-F indefinitely

CMV prophylaxis

Valcyte 900mg qd if normal renal function

CMV prophylaxis continue x 6 months

器官排斥之治療

在胰臟與腎臟同時移植的病人，當腎臟功能惡化時(肌酸酐 Creatinine 上升)，需懷疑器官排斥發生，同時回顧檢視免疫藥物劑量是否適當及病人是否有規則服藥，也需排除 CMV or BK virus 或其他感染所造成的腎臟功能惡化後，而後安排腎臟穿刺檢查來證實。

排斥反應根據 Banff class 分類，如下圖所示: (資料來源 UpToDate)

Banff diagnostic criteria for rejection and allograft nephropathy

1. Normal
2. Antibody-mediated rejection
Rejection: due, at least in part, to documented anti-donor antibody (suspicious for if antibody not demonstrated). May coincide with categories 3, 4 and 5 - see below
Type (grade)
1. ATN-like - C4d+, minimal inflammation
2. Capillary - C4d+, capillary margination and/or thrombosis
3. Arterial - C4d+, transmural arteritis (v3) (see section 4, grade III below)
3. Borderline changes
Suspicious for acute cellular rejection. No intimal arteritis ispresent, but there are foci of mile tubulitis (1-4 mononuclear cells/tubular cross-section). May coincide with categories 2 and 5
4. Acute/active cellular rejection
T-cell mediated rejection; may coincide with categories 2 and 5
Type (grade) of histopathological findings:
1A Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells)
1B Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross-section or group of 10 tubular cells)
2A Cases with mild to moderate intimal arteritis (v1)
2B Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
3 Cases with transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
5. Chronic/sclerosing allograft nephropathy
Fibrosing changes in the allograft, with or without features of true alloimmune injury to the graft; may coincide with categories 2, 3 and 4.
Grade 1
Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic (mild) rejection
Grade 2
Moderate interstitial fibrosis and tubular atrophy (a) or (b) (moderate)
Grade 3
Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b) (severe)
6. Other
Changes not considered to be due to rejection; may coincide with categories 2, 3, 4 and 5.

Modified from: Racusen, CR, Solez, K, Mihatsch, MJ, et al. Am J Transplant 2003; 3:708.

當排斥反應診斷確定後，治療原則如下：

Treatment for Acute Cellular Rejection (ACR)

對於 T cell-medicated rejection, Banff class 1A or 1B: 使用類固醇(3~5mg/kg)，靜脈注射 3~5 天，並調整 Tacrolimus 及 Mycophenolate 的劑量，對於治療效果不好的 Banff 1B 或是 Banff II-III 的排斥反應， 可使用 Thymoglobulin 3 mg/kg per day for three days or 1.5 mg/kg per day for five days (total dose 7.5 to 9 mg/kg)或是對於穿刺病理呈現 C4d 染色 negative 的病人，考慮再穿刺以排除 Antibody-medicated rejection(AMR).

以 UCSF 治療 ACR 的經驗:

Banff class 1A: Steroids

Banff class 1B 以上: Steroids + Thymoglobulin (6mg/kg)

Treatment for Antibody-Medicated Rejection (AMR)

(1) Antibody removal/neutralization: plasmapheresis, immunoadsorption, intravenous immunoglobulin, and splenectomy.
(2) Anti B-cell therapy: Mycophenolate mofetil, Rituximab, IVIG, and splenectomy.
(3) Antiplasma cell therapy: Bortezomib.
(4) Anti-T-cell therapies: T-cell depleting agents such as Antithymocyte globulin (ATG).
(5) Conversion to tacrolimus-based regimens.
(6) Terminal-complement pathway inhibitor: Eculizumab.

(J Transplant. 2012;2012:193724. doi: 10.1155/2012/193724)

以 UCSF 治療 AMR 的經驗:

Grade 1 & 2: Steroids and Thymoglobulin (6mg/kg) with/without IVIG

Grade 3: Plasmapheresis, IVIG (2g/kg), Steroids and Rituximab (375mg/m^2 one dose) or Eculizumab

GUIDELINES

a. We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)

b. We suggest treating subclinical and borderline cellular rejection. (2D)

c. We recommend using short duration high dose corticosteroids for the initial treatment of acute cellular rejection. (1D)

   i. We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)
   ii. We suggest using lymphocyte-depleting antibodies for resistant acute cellular rejection episodes and for acute cellular rejection episodes with a vascular component (BANFF Grade II or greater). (2C)

d. We suggest consideration be given to treating antibody-mediated acute rejection with plasma exchange and/or intravenous immunoglobulin. (2C)

e. For patients who have a rejection episode, we suggest increasing the baseline immunosuppression (e.g. adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate). Additional or alternative strategies include: adding a CNI if the patient is not taking this; switching cyclosporine to tacrolimus; switching an mTORi to a CNI; or increasing the dose of any of the immunosuppressive agents being used. (2D)

肆、建議

1．與泌尿外科組成腎胰移植小組:

因為本院腎臟移植是由泌尿外科醫師執行，而目前胰臟與腎臟同時移植的存活率最高，所以需要與泌尿外科合作組成腎胰移植小組，共同照護移植後病人，藉由各專科經驗以提供優良醫療品質。

2.邀請藥劑師加入腎胰移植小組之病房查房:

移植後病人需長期服用免疫抑制及預防感染藥物，藥劑師加入查房可以提升住院病人用藥的安全性、避免藥物交互作用及減少藥物對移植腎臟的損害。

伍、 附件資料

研究進修證明

UNIVERSITY OF CALIFORNIA SAN FRANCISCO
SCHOOL OF MEDICINE

This is to certify that
Hao-Ming Chang, MD
has completed
A Scholarly Observership in Division of Transplant
July 1st, 2013 – December 31st, 2013

Sandy Feng, M.D., Ph.D.
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