Evidenced based medicine

UROLOGY

2012/06/18

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Clinical scenario

- 病人:李先生因糖尿病導致慢性腎衰竭，血液透析1年多，此次因HLA配對符合，前來做腎臟移植

- 病人很擔心排斥問題導致移植失敗

提出background questions

- How to choose immunosuppressive therapy in renal transplantation in adults to reduce acute rejection

- recommend the administration of maintenance immunosuppressive therapy to kidney allograft recipients (Grade 1A). The optimal immunosuppressive regimen is unclear
- recommend induction therapy that consists of an antibody plus standard immunosuppressive therapy rather than standard immunosuppressive therapy alone (Grade 1A)

Current immunosupressive therapy for renal transplantation

- **Maintenance immunosuppressive therapy in renal transplantation—(**consisting of triple immunosuppression**)**
  - calcineurin inhibitor (cyclosporine or tacrolimus)
  - anti-metabolite (azathioprine or mycophenolate mofetil or Mycophenolate sodium)
  - prednisone

- A large number of combinations of immunosuppressive agents have been evaluated in randomized controlled trials.

- Include triple immunosuppressive therapy (calcineurin inhibitor, anti-metabolite, and corticosteroids), double immunosuppressive therapy with different combinations, and single agent therapy, generally with a calcineurin inhibitor

提出foreground questions

- Which calcineurin inhibitor (cyclosporine or tacrolimus) is better in reduce acute renal rejection?

EBM五大步驟

- Asking
  - 將病人的問題寫成PICO
- Acquire
  - 找資料來回答問題
- Appraisal
  - 嚴格評讀文獻
- Apply
  - 是否可應用到病人身上
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P Patient/Problem	Patient who receive renal transplantation
I Intervention	tacrolimus
C Comparison	cyclosporine
O Outcome	Reduce acute renal rejection

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Searching Strategy 1 : Finding out The Correct Keywords

- Use MeSHterm help identify terms

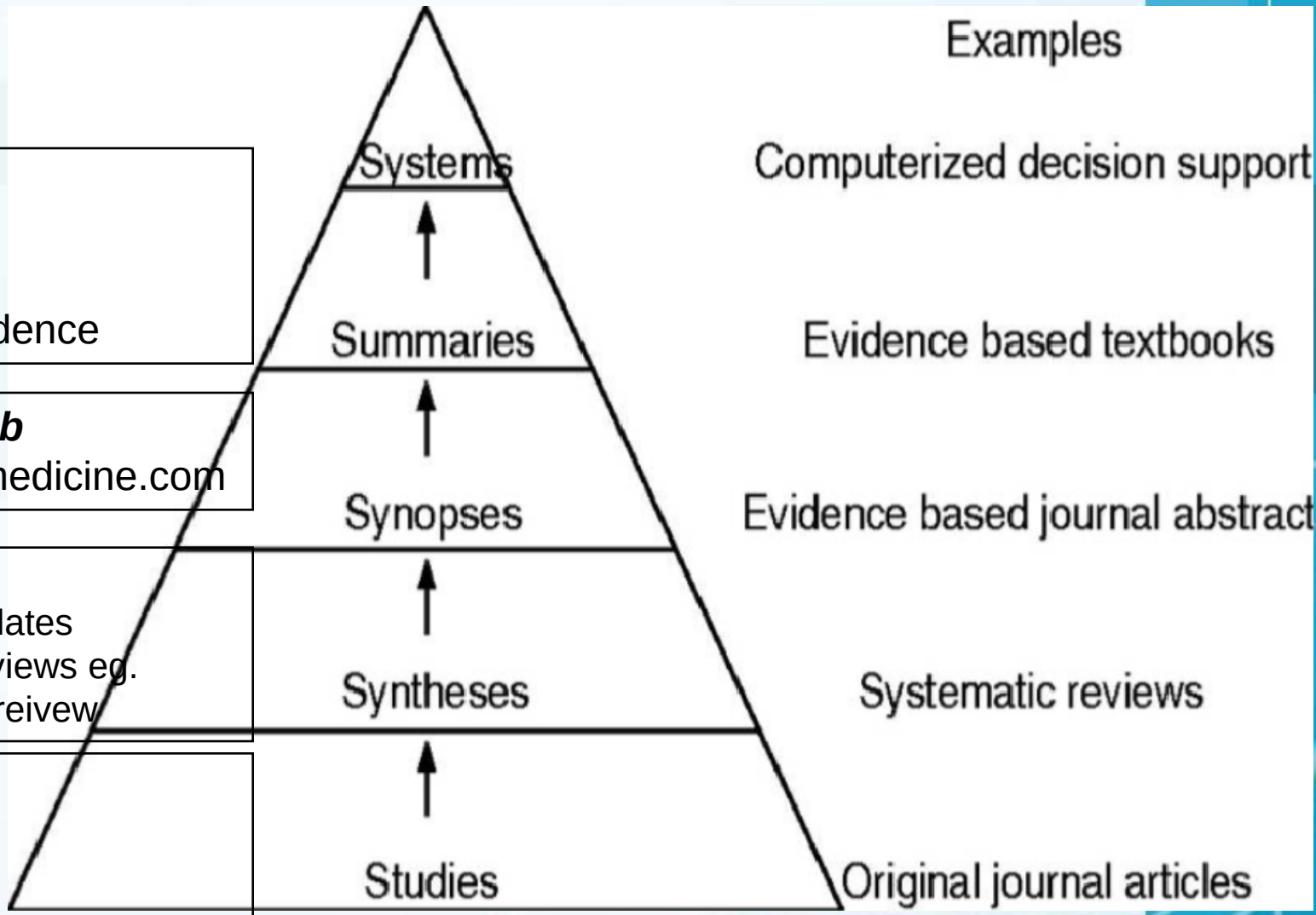
Search Strategy2

- 先從已經過評讀的secondary database開始找起(system, synopses, synthesis)

- 最後再找尚未經過嚴格評讀的study

”The 5S” Levels

The "5S" levels of organisation of evidence from healthcare research
Brian Haynes, R Evid Based Med 2006;11:162-164



UpToDate
DynaMed
ACP PIER
BMJ Clinical Evidence

ACP journal club
Evidencebasedmedicine.com

Cochrane Library
BMJ Evidence Updates
Other Systemic reviews eg.
PubMed systemic reivew

PubMed
SUMsearch
TRIP
Google

Keywords from PICO item

- MeSH terms：
- Renal transplantation->**Kidney Transplantation**

Summary

- Key word: renal transplantation, calcineurin inhibitor, tacrolimus cyclosporin
- Search over

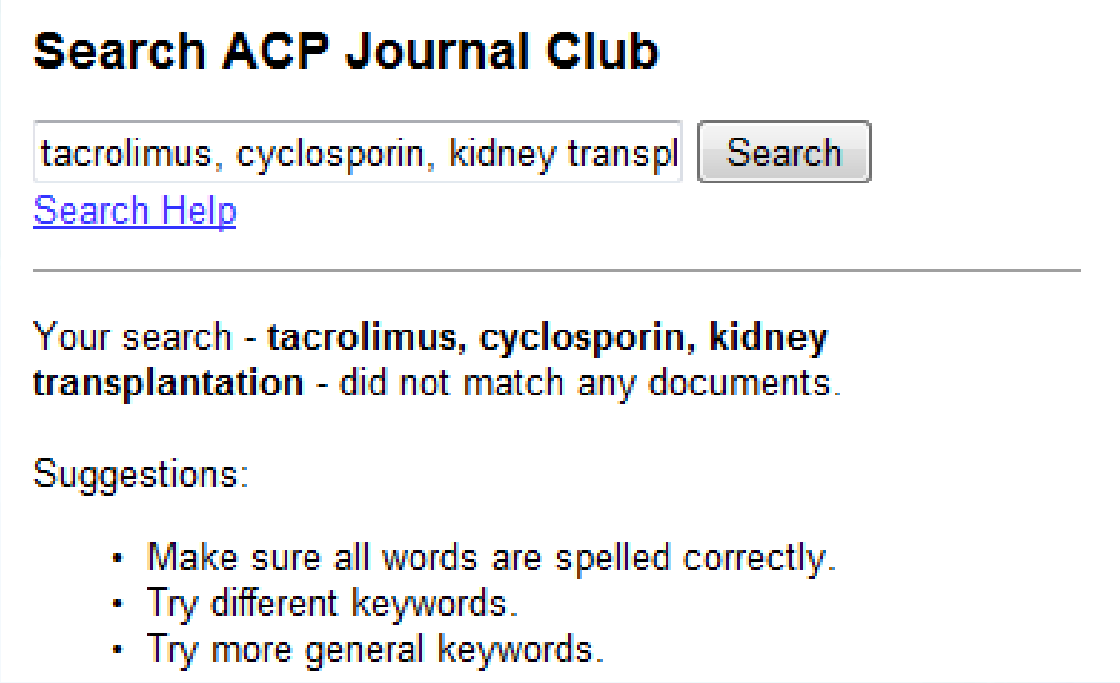
Data base	Uptodate
Title of article	**Maintenance immunosuppressive therapy in renal transplantation in adults**
content	meta-analysis and meta-regression was performed based upon 30 trials consisting of 4102 patients. **Tacrolimus** was associated with a significantly lower risk of allograft loss at six months (RR of 0.56, CI 95% 0.36 to 0.86), which was independent of cyclosporine formulation or concentration but was diminished with increased doses of tacrolimus.

Data base	Dynamed
Title of article	Reduced exposure to calcineurin inhibitors in renal transplantation
content	.based on randomized trial .1,645 renal-transplant recipients given daclizumab, mycophenolate mofetil and corticosteroids .low-dose tacrolimus associated with higher rates of allograft survival and lower rates of acute rejection than 3 other regimens (low- or standard-dose cyclosporine or low-dose sirolimus)

synopses

ACP Journal Club℠
The Best New Evidence for Patient Care

- Key word: tacrolimus, cyclosporin, kidney transplantation



- Result: no match

Synthesis

Data base	Cochrane
Title of article	Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients
content	**Tacrolimus** is superior to cyclosporin in **improving graft survival and preventing acute rejection** after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects.

Additional results of meta-analysis: acute rejection

Outcome, by time after transplantation	No of trials	No of participants	Relative risk (95% CI)*
Acute rejection (all)			
Three months	5	248	0.95 (0.44 to 2.08)
Six months	10	1778	0.68 (0.60 to 0.78)
One year	14	2751	0.69 (0.60 to 0.79)
Acute rejection (biopsy proved)			
Six months	7	1605	0.68 (0.48 to 0.96)
One year	8	1944	0.61 (0.52 to 0.72)

Study

- Mesh: tacrolimus, cyclosporin, kidney transplantation
- Limit: Publication dates 5 years, species Human, systemic review, English
- Result: 4 → 2篇相關

The role of tacrolimus in renal transplantation.

- Over the last decade tacrolimus has become the calcineurin inhibitor of choice for the prevention of rejection in renal transplantation.
- The objective of this study was to provide a review and update of the literature on the use of tacrolimus in renal transplantation.

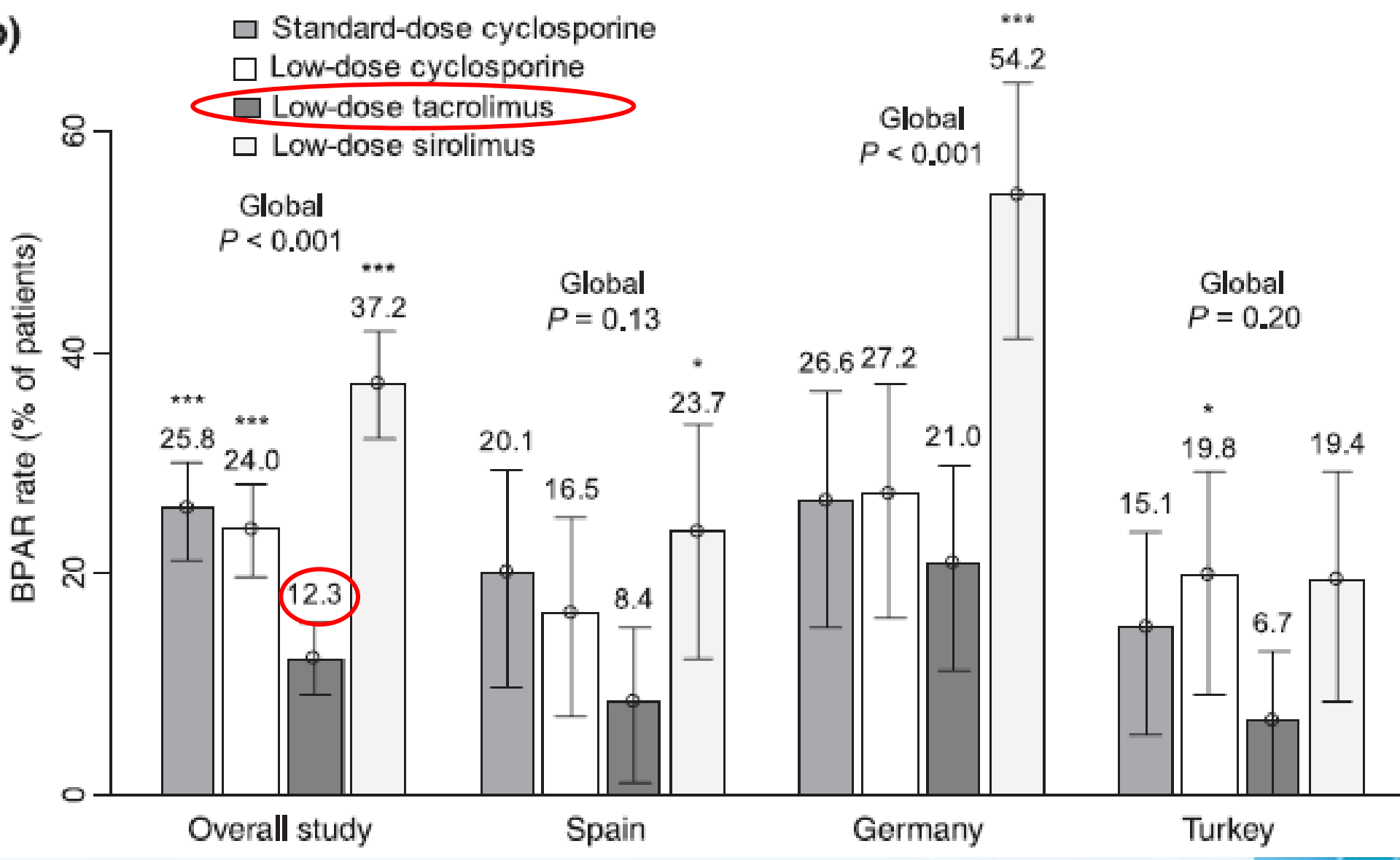
- Numerous clinical trials have shown tacrolimus to be superior to cyclosporine in the prevention of **acute rejection** and recent trials have demonstrated superiority of tacrolimus over cyclosporine in terms of **allograft survival**.

Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study

- De novo adult renal transplant recipients (n = 1645) were randomized to receive
  - **standard-dose cyclosporine,** or
  - **daclizumab induction plus low-dose cyclosporine**, or
  - **low-dose tacrolimus,** or
  - **low-dose sirolimus**,
- all in addition to mycophenolate mofetil and steroids

- Data for the highest patient-recruiting countries, Spain (n = 275),Germany (n = 316) and Turkey (n = 258), were compared
- Efficacy results for the three countries were consistent with that of the overall study - renal function and biopsy-proven acute rejection (BPAR)rates were superior with **low-dose tacrolimus**.

- **Turkey** had higher mean calculated glomerular filtration rate across all treatment groups (60.6-72.2 ml/min)compared with that of **Spain** (51.1-57.5 ml/min) and **Germany** (51.3-62.9 ml/min).
- **Spain** and **Turkey** had lower BPAR rates across the four treatment groups compared with the overall study; **Germany** had much higher rates(21.0-54.2%).
- These findings highlight the importance of inclusion of patients from different geographic origins in randomized clinical trials.



*P<0.05,**P<0.01,***P<0.001

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Appraisal (嚴格評讀)

- 對找到的文章進行**CRITICAL APRASIAL**

Level of evidence -Uptodate

level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Level of evidence -Dynamed

level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
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Level of evidence -Cochrane

level	與[治療/預防/病因/危害]有關的文獻
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Level of evidence -Pubmed

level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
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Apply

- 結合醫學倫理方法將**STUDY**的結果應用在病人身上

尊重與充分告知，做出臨床決定

醫療現況	病人意願
根據實證醫學的結果，Tacrolimus比cyclosporin對病人的急性排斥已移植腎臟之存活率更有幫助	病人願意先接受Tacrolimus的用藥
生活品質	社會脈絡
可以增加移植存活的機會，減低短期內再血液透析的機率	後續持續追蹤血液濃度以維持理想的抗排斥效果

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Audit

- 自我評估

在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？是，可以作爲治療參考。
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICO？可
  - 我的background question是否包括what, when, how, who等字根？無
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？知道
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？ 有

在「搜尋最佳證據」方面的自我評估

- 我是否已盡全力搜尋？是
- 我是否知道我的問題的最佳證據來源？是
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？學校資源便利。
- 我是否在搜尋上愈來愈熟練了？是。
- 我會使用「斷字」、布林邏輯、同義詞、MeSHterm，限制（limiters)等方法來搜尋？會。
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？需要加強

改變「醫療行爲」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？無
- 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？根據實證醫學的結果，更能說服病人接受Tacrolimus的使用與定期追蹤維持濃度 。

Thank your for your attention

Tacrolimus side effect

- Adverse Reactions Significant As reported for kidney, liver, and heart transplantation:
- ≥15%:
- Cardiovascular: Hypertension (13% to 62%), edema (peripheral 11% to 36%), chest pain (19%), edema (18%), pericardial effusion (heart transplant 15%)
- Central nervous system: Headache (24% to 64%), insomnia (30% to 64%), pain (24% to 63%), fever (19% to 48%), postprocedural pain (kidney transplant 29%), dizziness (19%)
- Dermatologic: Pruritus (15% to 36%), rash (10% to 24%)
- Endocrine & metabolic: New-onset diabetes after transplant (75% kidney transplant), hypophosphatemia (28% to 49%), hypomagnesemia (16% to 48%), hyperglycemia (21% to 47%), hyperkalemia (13% to 45%), hyperlipemia (10% to 31%), hypokalemia (13% to 29%), diabetes mellitus (24% to 26%), post-transplant diabetes mellitus (heart transplant 13% to 22%; kidney transplant 20%; liver transplant 11% to 18%)

- Gastrointestinal: Diarrhea (25% to 72%), abdominal pain (29% to 59%), nausea (32% to 46%), constipation (23% to 36%), anorexia (7% to 34%), vomiting (14% to 29%), dyspepsia (18% to 28%)
- Genitourinary: Urinary tract infection (16% to 34%)
- Hematologic: Anemia (5% to 50%), leukopenia (13% to 48%), leukocytosis (8% to 32%), thrombocytopenia (14% to 24%)
- Hepatic: Liver function tests abnormal (6% to 36%), ascites (7% to 27%)
- Local: Incision site complication (kidney transplant 28%)
- Neuromuscular & skeletal: Tremor (15% to 56%; heart transplant 15%), weakness (11% to 52%), paresthesia (17% to 40%), back pain (17% to 30%), arthralgia (25%)
- Renal: Abnormal kidney function (36% to 56%), creatinine increased (23% to 45%), BUN increased (12% to 30%), oliguria (18% to 19%)
- Respiratory: Atelectasis (5% to 28%), pleural effusion (30% to 36%), dyspnea (5% to 29%), cough increased (18%), bronchitis (17%)
- Miscellaneous: Infection (24% to 45%), CMV infection (heart transplant 32%), graft dysfunction (kidney transplant 24%)