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BRIEF ARTICLE

Effect of ureteric stents on urological infection and graft function following renal transplantation

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Abstract

AIM: To compare urological infections in patients with or without stents following transplantation and to determine the effect of such infections on graft function.

METHODS: All 285 recipients of kidney transplantation at our centre between 2006 and 2010 were included in the study. Detailed information including stent use and transplant function was collected prospectively and analysed retrospectively. The diagnosis of urinary tract infection was made on the basis of compatible symptoms supported by urinalysis and/or microbiological culture. Graft function, estimated glomerular filtration rate and creatinine at 6 mo and 12 mo, immediate graft function and infection rates were compared between those with a stent or without a stent.

RESULTS: Overall, 196 (183 during initial procedure, 13 at reoperation) patients were stented following transplantation. The overall urine leak rate was 4.3% (12/277) with no difference between those with or without stents - 7/183 *vs* 5/102, $P = 0.746$. Overall, 54% (99/183) of stented patients developed a urological infection compared to 38.1% (32/84) of those without stents ($P = 0.0151$). All 18 major urological infections occurred in those with stents. The use of stent (Wald $\chi^2 = 5.505$, $P = 0.019$) and diabetes mellitus (Wald $\chi^2 = 5.197$, $P = 0.023$) were found to have significant influence on urological infection rates on multivariate analysis. There were no deaths or graft losses due to infection. Stenting was associated with poorer transplant function at 12 mo.

CONCLUSION: Stents increase the risks of urological infections and have a detrimental effect on early to medium term renal transplant function.

Key words: Urological infection; Ureteric stent; Renal transplantation; Creatinine; Estimated glomerular filtration rate

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INTRODUCTION

Stents are used to protect the ureter-bladder anastomosis when performing renal transplantation in order to avoid or reduce urological complications[1-5]. The insertion of a stent does not eliminate the risk of complications, particularly urinary leak but may alter the approach to managing them[6]. Due to immunosuppression, stenting in transplant patients increases the risk of urological or blood stream infections[7,8]. As a result, opinion continues to be divided between those who routinely stent and those who only do so selectively on the basis of clear indications[2,9,10-13]. Proponents of selective stenting state that the associated risks are high enough to avoid rou-

tine stenting and advocate that careful surgical technique with selective stenting of problematic anastomoses yields similar results[12,13].

The key question is to determine what effect the increased risk of urological infection with stenting has on the early and medium term outcome of renal transplantation. This study was carried out to compare the incidence of urological infection in patients with or without stents inserted at transplantation and to determine the effect of urinary tract infections (MUI) in the early post transplantation period on short and medium term graft function.

MATERIALS AND METHODS

All recipients of kidney transplantation at the South West Transplant Centre (SWTC), Derriford Hospital, Plymouth between January 2006 and December 2010 were included in the study. Patient data was entered prospectively into the renal computer database (PROTON Information System, Clinical Computing PLC, London, United Kingdom) that was also used for information on patients handed over to other centres for follow up. Patients who developed significant urological complications after hand back to their home units were referred back to the SWTC for management and included in this analysis. Transplant nurses at peripheral centres were contacted to provide information on those patients whose data were incomplete. The duration of follow up ranged from 12 mo to 72 mo.

Patients were managed according to the standard protocol of the SWTC. Immunosuppression comprised basiliximab (induction), tacrolimus (0.1 mg/kg per day), mycophenolic acid (2 g/d) and prednisolone. Antibiotic prophylaxis included a single intravenous dose of augumentin 1.2 g at anaesthetic induction and a daily dose of co-trimoxazole 480 mg for 3 mo. At surgery, a 6-French, 12 cm, double pigtail ureteral stent (Cook Medical) was inserted at the discretion of the operating surgeon to establish internal drainage from the uretero-pelvic junction to the bladder. The transplant nurse practitioner would identify patients requiring stent removal and refer them to the urology nurse practitioners as soon as possible following transplantation. The stent was removed by flexible cystoscopy under local anaesthetic on a day case basis by a urologist. The duration of retention of routinely placed stents was progressively decreased from six weeks (initially) to two weeks in the latter phase of the study. Selectively inserted stents were removed after the duration advised by the transplant surgeon (usually 4-6 wk). In the latter part of the study period, a single intravenous prophylactic dose of antibiotics was administered prior to stent removal - usually gentamicin 3 mg/kg (rounded to the nearest convenient multiple of 40 and a maximum dose of 160 mg). If there were serious difficulties with venous access, the dose was given intramuscularly 30 min before the procedure. A mid stream specimen of urine was sent 48 h prior to removal of stent and this was repeated if blood or protein was present in urine or the patient was symptomatic.

The diagnosis of UTI was made on the basis of compatible symptoms supported by urinalysis and/or microbiological culture. Major urological infections (MUIs) included complicated UTI, pyelonephritis and urosepsis with or without bacteraemia. Delayed graft function (DGF) was defined as requirement for dialysis within the first week of transplantation. Primary non function (PNF) was defined as a graft that never worked or that never allowed the recipient to come off dialysis.

Relevant data including age, type and date of transplant, recognised risk factors for urological complications (stripped ureter, damaged renal arteries/bench surgery, multiple renal arteries, cold ischaemic time greater than 24 h, lower urinary tract obstruction and bladder abnormality) or risk factors for infection such as diabetes, reoperation and peritoneal dialysis associated peritonitis were entered into proforma sheets. This data was then transferred to an Microsoft Excel worksheet and analysed using SPSS 17® for Windows (SPSS Inc, Chicago, IL).

Statistical analysis

Early and late graft function, estimated glomerular filtration rate (eGFR) and creatinine (Cr) at 6 mo (Cr_6, $eGFR_6$) and 12 mo (Cr_{12}, $eGFR_{12}$), immediate graft function, graft outcome, infection rates, type of infection and urine leak were compared between those with a stent (ST) or without a stent (WST). Differences between groups were tested by the χ^2 statistic. Correlation between duration of stenting, interval to infection after transplantation, number of infection episodes and Cr and eGFR at 6 mo and 12 mo were tested using Pearson's correlation statistics. Also, the General Linear Modelling multivariate analysis of categorical variables [stent use; type of transplant - donation after circulatory death (DCD), donation after brain death (DBD) or living donation (LD); transplant number - whether first, second or third; diabetes; ureteric reflux; body mass index (BMI) > 30 kg/m^2; and early transplant outcome - immediate function, DGF and PNF] affecting urological infection following transplantation was performed. A P value of < 0.05 was taken as significant.

RESULTS

A total of 285 renal transplants were performed during the period comprising 181 males (age, mean ± SE: 52.1 ± 1.0 years; median: 53.5 years) and 104 females (age, mean ± SE: 49.2 ± 1.2 years; median: 50.4 years) giving a male to female ratio of 1.7:1. The commonest causes of established renal failure were glomerulonephritis (14.7%), cystic kidney disease (14%), immunoglobulin A nephropathy (13.3%) and diabetic nephropathy (6.7%). The overwhelming majority of transplants (189, 66.3%) were from DCD donors, with living donors LD constituting 28%. Also, 240 of the 285 patients (84%) were undergoing their first transplants whereas 36 (13%) and 9 (3%) were having their second and third transplants respectively. Information about use of antibiotic prophylaxis prior to implantation was unavailable in 23 cases (8.1%)

Table 1 Indications for stent placement during the initial transplant procedure *n* (%)

Reason		Comments
Routine	159 (86.9)	
Ureter related	9 (4.9)	*e.g.*, Stripped ureter
Poor kidney perfusion	6 (3.3)	
Contracted/thin bladder	3 (1.6)	Compliance mismatch
Technical factors	3 (1.6)	*e.g.*, intra-abdominal implantation
Ileal conduit	1 (0.5)	
Small kidney	1 (0.5)	Concern about size of renal artery
Long cold ischaemia time (> 24 h)	1 (0.5)	
Total	183 (99.8)	

Table 2 Comparison of groups with or without stent at initial transplant procedure *n* (%)

Parameter	Stented group (*n* = 183)	Without stent group (*n* = 102)	*P* value
Gender (male)	118 (65)	63 (62)	0.648
Age (yr), mean ± SE	52.4 ± 1.0 (53.7)[1]	49.1 ± 1.3 (50.6)[1]	0.035
Diabetes	31 (17)	13 (13)	0.347
BMI > 30 kg/m^2	39 (21)	21 (21)	0.531
Vesico-ureteric reflux	11 (6)	14 (14)	0.031
First transplant	151 (83)	89 (87)	0.315
Type of transplant			
DCD	111 (61)	78 (77)	0.023
DBD	12 (7)	5 (5)	
LD	60 (33)	19 (19)	
Delayed graft function	55 (30)	35 (34)	0.595
Septrin	173 (99)	91 (93)	0.002
Urine leak	7 (4)	5 (5)	0.746
Ureter stenosis	6 (3)	7 (7)	0.359
Ureter necrosis	1 (0.5)	0 (0)	
Infection	91 (53)	40 (42)	0.075
Operation-infection interval (d)			
mean ± SE	28.1 ± 3.7	33.3 ± 6.2	0.451
Median	10.5	11.0	

[1]Median age in parenthesis. Figures in parenthesis indicate percentages (except for age), corrected for number with relevant data. BMI: Body mass index; DCD: Donation after circulatory death; DBD: Donation after brain death; LD: Living donation.

but of the remaining 262, 86% (226) had appropriate prophylaxis. Ninety seven percent received prophylactic co-trimoxazole for 3 mo after transplantation.

One hundred and two patients (35.8%) did not have a ureteric stent inserted during their initial transplant operation. The indications for stenting in the remaining 183 (64.2%) are shown in Table 1. The demographic and other characteristics of the ST and WST groups are compared in Table 2. Thirteen of the WST group were stented at subsequent re-exploration and re-implantation of the transplant ureter (stenosis/stricture in ten, urine leak in two and negative exploration in one). Five patients in the ST group received a stent at subsequent re-operation for a urological complication. Overall, 196 (68.8%) patients received a stent following renal transplantation, with 159 (81%) of these inserted routinely. The proportion of patients receiving stents at transplantation (irrespective of whether inserted during the initial operation or at re-operation) varied with the type of organ donor (DCD 54.5%; DBD 58.8% and LD 70.9%), the differences were statistically significant - Pearson $\chi^2 = 6.202$; $df = 2$; $P = 0.045$. The mean ± SE duration of stenting was 46.99 ± 7.6 d, which was lower for routine than selective indication (39 ± 4.4 d *vs* 83.4 ± 33.2 d, respectively).

If eight patients with no data regarding urine leak were excluded from analysis, then the overall urine leak rate was 4.3% (12/277). Five of 100 patients (5%) not having a stent inserted during their initial transplant suffered urine leak whereas seven of 177 (4%) in the ST group leaked - the difference in leak rates between the two groups was not statistically significant (Table 2). Similarly, the difference in the distribution of ureteric stenosis or necrosis between groups was not statistically significant (Table 2).

Excluding 18 patients with missing information regarding infection, 49% (131/267) of the patients had infection after transplantation, with the majority (87%) being UTI. Five patients (1.9%) had miscellaneous (non urological) infections. Micro-organisms were isolated in 131 (46%) patients. Infection was caused by multiple organisms in 32% (42/131) but *Escherichia coli* (21%) was the commonest single isolate. Other coliforms amounted to 23%, whereas Candida was cultured in 1.5% cases. Overall, 54% (99/183) of ST patients developed a urological infection compared to 38.1% (32/84) of the WST group and the difference was statistically significant ($\chi^2 = 5.900$; $df = 1$; $P = 0.0151$). However, with respect to the initial transplant procedure, the difference in infection rates between ST and WST groups was not statistically significant (Table 2). The difference in the distribution of infection types (UTI or MUI) between the ST and WST groups was statistically significant (Yate's $\chi^2 = 6.027$; $df = 1$; $P = 0.0141$). All 18 MUI (9 with urosepsis, 6 with pyelonephritis and 3 with bacteraemia) occurred in those with stents. Ureteric stenting was associated with poorer transplant function at 6 mo and 12 mo (Table 3).

One hundred and eighty three (64.2%) patients achieved immediate allograft function whereas 90 (31.6%) had DGF and 12 (4.2%) had PNF. There was no difference in the rate of DGF between the ST and WST groups (Table 2). By the end of the follow up period, 17 patients had died with a functioning graft and 37 allografts had failed (Figure 1). Although the cause of death was undetermined in six, none of the deaths were directly related to urological infection (cardiac in four, cancer in three, bowel infarction in two, cytomegalovirus infection and trauma in one case respectively.

Infection was more likely to occur in ST patients with DGF (73.7%; 42/57) than in those with immediate allograft function (45%; 54/120) and the difference was statistically significant ($\chi^2 = 12.810$; $df = 1$; $P = 0.0003$). Irrespective of stenting, the association between infection and immediate allograft function [41% (71/173)] or DGF [65% (56/86)] was found to be statistically significant (Fisher's exact test, $P = 0.0003$). However, the distribution of UTI and MUI between patients with DGF

Table 3 Effect of stent use on various outcome parameters, and infection and type of urological infection on allograft function

	Cr_6	Cr_{12}	$eGFR_6$	$eGFR_{12}$
Stent				
Yes				
mean ± SE	137.5 ± 4.6	139.7 ± 4.7	50.9 ± 1.3	49.9 ± 1.3
Median	123.5	125	52	49.5
n	180	176	180	176
No				
mean ± SE	132.4 ± 5.6	124.4 ± 5.4	52.1 ± 1.9	54.8 ± 2.1
Median	120.5	120	52	55
n	78	74	77	73
F-statistic	0.42	3.603	0.256	4.047
P value	0.517	0.059	0.614	0.045
Parameters				
Infection				
Yes				
mean ± SE	143.1 ± 6.2	144.0 ± 6.2	49.5 ± 1.6	48.9 ± 1.7
n	121	118	120	117
No				
mean ± SE	128.0 ± 4.0	125.5 ± 4.3	53.4 ± 1.4	54.4 ± 1.4
n	123	119	123	119
F-statistic	2.232	3.123	2.154	4.038
P value	0.109	0.046	0.118	0.019
Infection type				
UTI				
mean ± SE	140.6 ± 6.9	139.8 ± 6.8	50.2 ± 1.8	50.3 ± 1.8
n	105	104	104	103
MUI				
mean ± SE	156.4 ± 11.5	167.6 ± 11.6	45.8 ± 3.8	41.3 ± 3.7
n	18	16	18	16
F-statistic	0.558	1.299	0.524	1.783
P value	0.574	0.277	0.593	0.173

UTI: Urinary tract infection; MUI: Major urological infection; Cr_6: Creatinine at 6 mo; Cr_{12}: Creatinine at 12 mo; $eGFR_{12}$: Estimated glomerular filtration rate at 12 mo; $eGFR_6$: Estimated glomerular filtration rate at 6 mo.

and immediate function were not statistically significant (Yate's $\chi^2 = 0.054$, $df = 1$, $P = 0.8165$). Only the use of stent (Wald $\chi^2 = 5.505$, $df = 1$, $P = 0.019$), diabetes mellitus (Wald $\chi^2 = 5.197$, $df = 1$, $P = 0.023$) and a BMI > 30 kg/m^2 (Wald $\chi^2 = 3.801$, $df = 1$, $P = 0.051$) were shown to have significant influence on urological infection rates on multivariate analysis.

Stents inserted for ⩽ 30 d were associated with a higher infection rate of 58.3 % (49/84) compared to a rate of 48% (47/98) for those with stents longer than 30 d ($\chi^2 = 1.953$, $df = 1$, $P = 0.163$). The median time to infection in the ST group was 10.5 d (Table 2) with 75% of infections occurring by the 38th day postoperatively. The duration of ureteric stenting and transplant - infection interval had no significant correlation with Cr_6, Cr_{12}, $eGFR_6$ and $eGFR_{12}$. However, the number of infection episodes had a significant level of correlation with Cr_6, Cr_{12}, $eGFR_6$ and $eGFR_{12}$ [Pearson correlation (*PC*) = 0.175, $P = 0.008$; *PC* = 0.210, $P = 0.002$; *PC* = -0.174, $P = 0.009$; and *PC* = -0.231, $P = 0.001$ respectively]. Patients who developed urological infection had worse allograft function at 6 and 12 mo after transplantation with the differences reaching statistical significance at 12 mo (Table 3). Although patients with MUI had worse Cr and eGFR at 6 mo and 12 mo post transplantation, the differences were not statistically significant (Table 3).

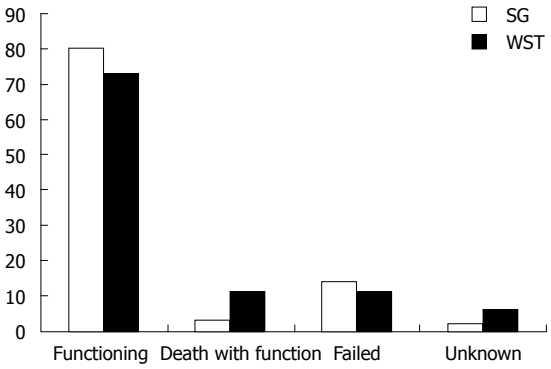

Figure 1 Outcome of 285 renal transplants according to whether patients were stented or without stent. SG: Stented group; WST: Without stent.

DISCUSSION

This observational study demonstrates the higher risk of infection in patients with ureteric stenting compared to those without (54% *vs* 38%) during renal transplantation - rates that are similar to other reports[7,8,12,14] but much higher than the 12% reported by Ashraf *et al*[15]. Branitz *et al*[16] and Ranganathan *et al*[1] not only showed a much higher infection rate in the stented group (76% *vs* 45% and 71% *vs* 39%, respectively), but also noted that patients who suffered a UTI while they had a stent in place were more likely to get further episodes of UTI after stent removal. In our study, all eighteen cases of MUI occurred in the stented group. This is similar to the finding by Branitz *et al*[16] of all 10 episodes of severe infection in their ST group. Though there were no graft losses or patient deaths secondary to MUIs and the rate of DGF in the patients with MUIs was not significantly different to other UTIs, MUIs were associated with poorer transplant function at 12 mo (Table 3). In a Cochrane review of seven randomised controlled trials (1154 patients), Wilson *et al*[2] found an increased risk of UTIs in stented patients (RR = 1.49, 95%CI: 1.04-2.15; with two kidneys lost to infections), but noted that this effect was neutralised by co-trimoxazole 480 mg daily. Argani *et al*[17] also demonstrated the role of prophylactic cotrimoxazole in reducing the incidence of UTI in stented patients. Prophylaxis with co-trimoxazole is standard practice at the author's centre (99% of the ST group received it) but no such beneficial effect was evident. However, there are several reports of a lower UTI rate in the ST group[18-20] or a similar infection rate in both groups[6].

The optimal duration of stenting in renal transplantation is not known. In this study the average duration for stenting over the period under consideration was 46 d. Although the duration of stenting did not significantly correlate with the risk of infection and had no statistically significant impact on Cr levels at 6 and 12 mo in our study, based on a median time to infection of 10.5 d, it would seem reasonable to remove all stents by 2 wk after insertion. This approach is similar to Verma *et al*[21]

who reported from a case controlled study that stenting for two weeks avoided the complications associated with prolonged stenting without compromising the benefits. Also, Tavakoli *et al*[14] showed that the rate of UTIs was increased, especially if stents were left in for more than 30 d although they advocated stent removal by 4 wk. Based on the understanding that routine placement of stents is aimed at keeping the ureteric anastomosis patent in the postoperative phase when inflammatory oedema is common, there is now a general trend towards early stent removal in order to avoid complications like infections. Dong *et al*[22] have reported a UTI rate of 4% (3/70) achieved by removing the stent along with the bladder catheter between the seventh and tenth post operative day. Sansalone *et al*[23] joined the stent and urinary catheter and removed both at 10 d post operatively demonstrating a lower complication rate when compared to those without stents (1.5% *vs* 4.1% $P < 0.0001$). The issue about how long to leave a stent in situ is an important one and possibly requires a randomized controlled trial to properly address it. Perhaps another way of reducing the infection complications of stents is through technological development of better materials to reduce or prevent bacterial adherence to the stents. Whether antibacterial coating/impregnation of stents would work is another question.

The finding that urine leak rate was not affected by the placement of ureteric stents (Table 2) in this series is similar to the report by Dharnidharka *et al*[8] who showed that stents offered no benefit in preventing ureteric stenosis or leaks, nor in improving graft survival. Some studies have demonstrated lower leak rates in the stented group[14,18,19,23,24] whereas Osman *et al*[12] found a small increase in leakage in the stented group (4% *vs* 0%) and a significant increase in UTIs (39.6% *vs* 18%, $P = 0.02$). Perhaps factors like stripping of the ureter, ureteric injury, multiple renal arteries, damage to lower polar artery, operative technique, cold ischaemia time and donor vascular disease are more important in determining whether urine leak or ureteric necrosis occurs or not. DuBay *et al*[25] while arguing the case that routine stent placement was inexpensive due to reduction in ureteric complications failed to consider the additional cost of infection related complications.

Review of the literature revealed a dearth of information on the effect of urological infections on subsequent transplant function, although bacteraemia in transplant recipients frequently originates in the urinary tract. An important finding in this study is the deleterious effect of multiple urological infections on transplant function. Whether this negative effect which was demonstrated even at 12 mo impacts on long term function as well needs to be studied in in a larger trial. In light of the fact that stents increase the rate of repeat UTIs[1,16] and the almost exclusive occurrence of MUIs in the stented group, stents may be exerting a harmful effect on graft function. This may in itself be a strong argument in favour of selective placement of stents and needs to be looked at in a larger randomised controlled trial.

A study of this nature has several limitations. The retrospective nature of this study limits its usefulness somewhat, but all the data were collected prospectively and recorded in a designated renal electronic database. In addition there were some gaps in the data, especially in the length of hospital stay, readmission rate, and the incidence of UTI prior to transplantation. This is partly due to the loss of patients to follow up and despite exhaustive efforts to individually chase all cases, data was unavailable from some of the outlying hospitals in the fairly large region covered by our centre. Also, it was not possible to determine the quantitative effect of infection on length of hospital stay or readmissions to hospital.

Notwithstanding the retrospective nature of this study, stents increase the risks of urological infections and appear to have a detrimental effect on early to medium term renal transplant function. Whether stents are used routinely or selectively, there is need to remove them early (< 2 wk) in order to reduce the risk of infection.

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COMMENTS

Background

Stents are used to protect the joining between the transplant ureter and the recipient's bladder when performing kidney transplantation in order to avoid or reduce complications. It is thought that using a stent in this way does not eliminate the risk of complications, particularly urinary leak may in fact increases the risk of urological or blood stream infections. As a result, opinion continues to be divided between those who routinely stent and those who only do so selectively on the basis of clear indications.

Research frontiers

There are several reports on the effect of ureter stenting for kidney transplant recipients but the key issues such as how long it should be retained in the body before removal, its effect on kidney function remain unanswered. There are also no well conducted randomised controlled trials to assess the effect of stents.

Innovations and breakthroughs

Proponents of selective stenting state that the associated risks are high enough to avoid routine stenting and advocate that careful surgical technique with selective stenting of problematic anastomoses yields similar results. The key question is to determine what effect the increased risk of urological infection with stenting has on the early and medium term outcome of renal transplantation. In the present study, authors compared the incidence of urological infection in patients with or without stents inserted at transplantation and report the effect of urinary tract infections (UTIs) in the early post transplantation period on short and medium term graft function

Applications

This study suggests that stents increase the risks of urological infections and have a detrimental effect on early to medium term kidney transplant function. It calls for a controlled trial to determine the optimum duration of retaining stents following insertion.

Terminology

A ureteric stent used for the purpose of kidney transplantation is a 6-French, 12 cm, double pigtail ureteral plastic tubing inserted to establish internal drainage from the ureter in to the bladder.The diagnosis of UTI was made on the basis of compatible symptoms such as discomfort during urination, urinary discharge, lower abdominal pain and fever supported by findings on urine strip test and/or microbiological culture. Major urological infections included complicated UTI,

pyelonephritis (infection extending to the kidneys) and urosepsis with or without bacteraemia (bacteria multiplying in the blood stream).

Peer review

Although there are minor recommendations that would be good for the authors if they revise the manuscript accordingly, the manuscript can also be published in this original form as well given the nature of the study which is not randomized.

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An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Data that are not statistically significant should not be noted. [a]$P < 0.05$, [b]$P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, [c]$P < 0.05$ and [d]$P < 0.01$ are used. A third series of P values can be expressed as [e]$P < 0.05$ and [f]$P < 0.01$. Other notes in tables or under illustrations should be expressed as [1]F, [2]F, [3]F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc*., in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23243641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.
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