Economic Evaluations of Organ Transplantations

A Systematic Literature Review

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Abstract: The purpose of this study is threefold; 1) to establish the current level of knowledge regarding cost-effectiveness of organ transplantation, 2) to identify knowledge gaps, and 3) to suggest a framework for future studies. A systematic literature review of economic evaluations of transplantations of solid organs was conducted in October 2010. Economic evaluations published since 2000 and reviews published since 1987 for kidney, liver, lung, heart, pancreas, and small bowel transplantations were collected. The studies were analysed regarding results and study characteristics. The review demonstrates a lack of economic evaluations for all included organ transplantations. The cost-effectiveness of kidney transplantation, and to some extent liver transplantation, compared to a non-transplant alternative appears to be established. However, cost-effectiveness for transplantation of lung, heart, pancreas, and small bowel can neither be established nor rejected based on earlier studies. Many of the included studies were limited in a number of ways; e.g. using short follow-up period, failing to account for sample selection in treatment groups, comparing to unrealistic alternatives, lacking important cost categories, and using a limiting perspective. Recommendation for future studies are, besides accounting for the above, to conduct sub-group analyses as patient and disease characteristics, among other things, has been shown to affect the cost-effectiveness of organ transplantation.

Keywords: Literature Review, Economic Evaluations, Organ Transplantation

1 Introduction

Over the last few decades, much thanks to improvements in immunosuppression therapy, organ transplantation has evolved from an experimental treatment to become the gold standard for a number of ailments, such as end-stage cardiomyopathy (Williams et al 2008).[1] The cost of transplantation has generally fallen over time, while survival and quality of life have improved (O'Grady 1997). This indicates that the cost-effectiveness of transplantation has also improved over this period. It is therefore important to have up-to-date estimates of the cost-effectiveness of organ transplantations, in order to ensure that society's scarce resources are used in a manner that maximises societal health and corresponds to current treatment practise.

Organ transplantation is also an interesting issue in health economics due to the distinct scarcity of organs, which makes the opportunity cost obvious; misallocation of

[1] This literature review has also been published in Swedish (Jarl & Gerdtham 2011).

organs to sub-optimal patient groups clearly has an alternative better use. Thus economic evaluations are useful tools to establish priority settings in order to maximise societal utility (health). However, since disease structures as well as treatments (and their effectiveness) change significantly over time, it is vital to continuously update estimations of the cost-effectiveness of transplantation.

The actual number of transplantations performed is continuously increasing. Due to the difficulty of conducting randomised control trials in the area, a large sample size is required to avoid estimation bias (see below). It is therefore to be expected that the possibility of conducting appropriate economic evaluations will improve over time. Thus, updating prior cost-effectiveness studies has the additional benefit of potentially improving the estimations.

The aim of the current study is threefold. The first objective is to establish current knowledge regarding the cost-effectiveness of organ transplantation, the second is to identify gaps in knowledge that require more research, and the third is to suggest a framework for future studies. The focus is on organ transplantation as such, rather than on specific parts of the transplantation process (e.g. use of different immunosuppressants), and non-transplantation treatments are used as comparison alternatives.

The methods used in this review are described below. This is followed by the results one transplantation area at a time, starting with the kidney. The article ends with a discussion of the current state of economic evaluations of organ transplantation in general, and ways forward for future research. A detailed description of each included study is available in the appendix.

The review finds that there is a general lack of economic evaluations in the organ transplantation area. Although renal transplantation appears to be both cost-effective and cost-saving compared to dialysis, and liver transplantation cost-effective, methodological problems suggest that future research should re-visit these areas. For all other studied organ transplantation types not enough information was available to determine the cost-effectiveness. Common methodological issues include, but are not limited to, missing cost-categories, limited perspectives, reduced follow-up, and lack of sub-group analyses. More research is needed in all areas, using health economic theory and methods.

2 Method

A systematic literature search was conducted in October 2010 in PubMed (U.S. National Library of Medicine) and the NHS Economic Evaluation Database (Centre for Reviews and Dissemination, University of York). Both databases were broadly searched using combinations of the following terms: transplant, transplantation, organ transplant, cost-effectiveness, cost-benefit, cost-utility, cost-minimization, cost-minimisation, and economic evaluation. We also searched the reference lists of relevant studies identified through the database search.

The inclusion criteria were that the studies should be economic evaluations of transplants as such, should have been published in 2000 or later (although reviews were collected from 1987), should concern humans, and should be written in English. The following exclusion restrictions were applied:

- No studies regarding stem cell and/or bone marrow transplantation.
- No studies regarding transplantation from the patient's own body (allograft).
- No studies with artificial or non-human tissue (xenograft).
- No studies comparing one transplant procedure to another – unless cost-effectiveness compared to a non-transplantation scenario was also included.

- No studies on donor programs to increase available grafts.
- No studies regarding bridge-to-transplantation.

In other words, the focus was on allograft solid organ transplantation, compared to (gold standard) non-transplantation treatment. The main reason for focusing on studies published after 1999 was the fall in costs over time resulting from technical progress. At the same time as the costs have fallen, the outcomes have greatly improved, from a time when transplantations were considered experimental treatments to recent years in which they are common practice (see for example O'Grady (1997) for liver, Winkelmayer et al (2002) for kidney, and Schulak et al (2001) for pancreas transplantation). We therefore consider early studies to have limited relevance for today's situation. The cut-off point used here is arbitrary, but the risk of excluding relevant information is mitigated by the fact that reviews covering earlier studies were included when available. It is of course possible that the cost-effectiveness has changed over the 10 years this study covers. However, as will be shown in the results, few studies combined with large differences in method and approach makes a trend analysis impossible.

There is still no consensus on what is considered cost-effective; that is, what is worth the resources spent in terms of outcome in comparison to an alternative treatment. Traditionally, especially in the USA, a cost-effectiveness ratio below US$50,000 per quality-adjusted life-year (QALY) has been considered to be cost-effective. This figure comes from the ratio for dialysis following end-stage renal failure (Eichler et al 2004). Interestingly, even though this figure is several decades old, it is still used unmodified. If adjusted for inflation, it would be around US$100,000 in today's values (Machnicki et al 2006). However, this is by no means the only suggested threshold, and many country-specific values have been developed. For example, the current Swedish recommendation for cardiac care is that a cost/QALY below US$11,300 (SEK 100,000) should be considered low, one of US$11,300-56,700 should be considered moderate, one of US$ 56,700-113,400 should be considered high, and one above US$113,400 should be considered very high (Swedish National Board of Health and Welfare 2008). The WHO suggests using a figure of 1-3 times the country's GDP per capita (WHO 2010). Here, we present all results in US$ in 2009 prices, although the original values as reported in the studies are also included in the tables below. When specific studies are discussed, their conclusions are also presented, and these are often in relation to the traditional cost-effectiveness ratio of US$50,000/QALY. It is however important to remember that cost-effectiveness is a relative concept, which requires a comparison. All currency conversions were performed according to the PPP for BNP (OECD 2010) and then adjusted according to the US consumer price index for medical care (US Labor Department 2010). For studies which did not state which year's prices their results were shown in, we assumed a price year of two years before publication. Where prices for several years were used, we calculated an unweighted average.

2.1 Issues in organ transplantations

There are a few inherent problems with economic evaluations of organ transplantations. Firstly, randomised control trials are not available, for ethical reasons among others. The result of this is that the transplant and the alternative (non-transplant) cohorts are different in many aspects, such as severity of disease, socioeconomic and demographic characteristics, and the capacity to benefit from the procedure. One method to account for this is the modelling approach, in which the natural history of a transplant patient is estimated as if the transplantation had not taken place. This has its own problems,

especially as the model will never be better than the available information. Secondly, the transplantation procedures for the same organ transplantation can differ between countries or even between health care units. Examples of this could be the use of immunosuppressants, the severity of disease among patients, the organ allocation scheme, and the number and quality of donated organs. All of these factors have the potential to affect cost-effectiveness, making comparison between studies difficult. These issues will not be discussed in connection to the studies included below, but will be commented on in the discussion section.

3 Results

The relevant studies found in the systematic literature search are presented here in tables along with their findings on cost-effectiveness of organ transplantations. Commentary and conclusion are supplied for each organ separately. Detailed description of each identified review on the subject published since 1987 and individual economic evaluation published since 2000 can be found in the appendix.

3.1 Kidney transplantation

Several economic evaluations regarding the cost-effectiveness of renal transplantation (KTx), and reviews of such studies, have been performed. Those identified in this review are presented in Table 1a-b and in appendix.

Based on the available information, it appears that renal transplantation is both cheaper and more effective than dialysis. Renal transplantation should thus be expanded to replace dialysis treatment, as this will both save resources in the health care sector and improve health outcomes for the patients. However, some of the studies also indicate that the cost-effectiveness ratio will differ between different population subgroups. Examples of factors that affect the cost-effectiveness of KTx include the quality of the donated kidney, and patient characteristics such as age and co-morbidity (e.g. Verheijde et al 2008; Quinn et al 2007; Jassal et al 2003). It is thus likely that renal transplantation is not cost-saving for certain groups, and might even be considered not cost-effective at all for some. Any proposed expansion of the transplantation service must take this into consideration.

A rather common assumption in earlier studies is that life expectancy without end-stage renal treatment is non-existent (Winkelmayer et al 2002), and hence that the alternative for comparison to KTx carries no costs and no benefits (i.e. immediate death). Although this assumption might once have been valid, it should now be questioned given that treatment today generally occurs at an earlier phase of the disease (Winkelmayer et al 2002), not to mention the unrealism of such alternative. However, this also highlights another factor that could be expected to influence the cost-effectiveness ratio, namely how early in the disease process a transplantation takes place. This is obviously connected to the waiting time for an organ which is in limited supply, a factor which has been shown to affect the cost-effectiveness of transplantations in the elderly (Jassal et al 2003).

Many of these studies consider the costs and effects of renal treatment over the entirety of the patient's remaining life, but others consider them for only a certain number of years. This restricted follow-up time affects the cost-effectiveness ratio, and should therefore be avoided. Another issue worth noting is that some of the studies focus solely on successful transplantations. For an economic evaluation to give correct and unbiased results, it is necessary to also include the costs and effects of failed transplantations. In addition, it is of limited interest simply to know that successful transplantations are cost-effective. It is not always easy to determine the extent to which the different studies

account for unsuccessful transplantations, and so the effect this might or might not have on the general conclusions cannot be further commented on.

Living donor renal transplantation appears to be more cost-effective than deceased donor transplantation, especially among the elderly. This is most likely connected to a reduction in waiting time, which would be spent on dialysis. It should be noted that not all of the studies of living donor transplantation take into account the costs and/or increased risk for the donor. This might reduce the cost-effectiveness, although recent advances in surgical procedures to procure the organ, for example laparoscopic nephrectomy, will probably reduce the adverse effects (e.g. Kok et al 2007).

The review by Winkelmayer et al (2002) (see appendix) highlights two areas for future research; 1) calculating correct (unbiased) incremental cost-effectiveness for different treatments (an issue discussed further below), and 2) including all relevant cost and benefits including the patient's and informal caregiver's time. This generally still stands, although we would add that future studies in this field should also focus on population subgroup analyses and transplantation procedure factors such as waiting time and organ quality. In addition, it is important that more studies are conducted from a societal viewpoint, including wider costs such as labour productivity and informal care. Most of the studies included here have a health care provider or health care payer perspective. The study by Cleemput et al (2004) raises the question of the extent to which the reduced costs and benefits of non-adherence following transplantation have been accounted for in existing economic evaluations. For example, one might ask whether the data used in current Markov models are based on a combination of adherent and non-adherent patients, or instead dominated by one of the two. This could cause discrepancies between the cost-effectiveness calculations reported in studies, and real world application of transplantation programmes.

Table 1a. Economic evaluations of kidney transplantations.

	Country	Year	N	Type of study	Approach	Perspective	Alternative
Kontodimopoulos & Niakas 2008	Greece	Not stated	874 for estimation of outcome	Survey/ retrospective	Cost-utility	Not stated	Not stated (immediate death)
Quinn et al 2007	North America	Not stated	NA	Markov model	Cost-utility	Health care	Dialysis
Whiting et al 2004	Canada	Not stated	NA	Markov model	Cost-utility	Health care payer	Dialysis
Matas & Schnitzler 2003	USA	1995-1999	NA	Markov model	Cost-utility	Societal	Dialysis
Perovic & Jankovic 2009	Serbia	2008	150 (50 KTx)	Not stated	Cost-utility	Health care payer	Dialysis
Schweitzer et al 2007	USA	2002	NA	Markov model	Cost-utility	Not stated	NA
Cleemput et al 2004	Belgium	1999-2002	NA	Markov model	Cost-utility	Societal	Dialysis
Greiner et al 2001	Germany	1993-2004	1149 (169/77 KTx)	Prospective	Cost-utility	Societal (?)	Dialysis
Kaminota 2001	Japan	1995	26 233 (604 KTx)	Retrospective (?)	Cost-utility	Health care payer (?)	No treatment (dialysis)
Jassal et al 2003	NA	NA	NA	Markov model	Cost-utility	Health care payer	Dialysis
Kaló et al 2001	Hungary	1994	1082 (242 KTx)	Retrospective	Cost-effectiveness	Health care payer	Dialysis

Table 1b. Economic evaluations of kidney transplantations.

	Outcome	**Follow-up**	**Discounting**	**Cost-effectiveness** (US$)	**Comments**
Kontodimopoulos & Niakas 2008	QALY	Lifetime	5%	17,300/QALY (€11,981)	Clear focus on successful transplantation.
Quinn et al 2007	QALY	25 years	Yes, but rate not stated	Cost saving: 183,900 (CA$192,093) per patient	Clear focus on successful transplantation. Age group analyses.
Whiting et al 2004	QALY	20 years	5%	Cost saving: 15,400 (CA$14,438) per patient	
Matas & Schnitzler 2003	QALY	20 years	5%	Cost saving: 124,400 (US$94,579) per patient	Does not account for the increased risk for living donors.
Perovic & Jankovic 2009	QALY	10 years	3% (costs only)	Cost saving: 148,100 (€116,385) per patient	
Schweitzer et al 2007	QALY	20 years	3%	Normal risk-kidney: 78,900/QALY (US$60,000) Increased risk-kidney: 93,400/QALY (US$71,000)	Transplantation of increased-risk kidneys compared with normal kidneys, therefore no relevant alternative given.
Cleemput et al 2004	QALY	Lifetime (?)	3%	Adherence: cost saving: 79,900 (€48,717) per patient Non-adherence: cost saving: 142,500 (€86,897) per patient ICER adherence vs. non-adherence: 57,400 (€35 021)	Small sample, especially for non-adherence.
Greiner et al 2001	QALY	20 years	5%	KTx: 58,900 /QALY (DM38,300) Dialysis: 227,200/QALY (DM147,800)	Also estimates productivity losses.
Kaminota 2001	DALY	Lifetime	3%	LDKTx: 17,600/DALY (¥1,809,000) DDKTx: 22,500/DALY (¥2,322,000) Dialysis: 91,800/DALY (¥9,456,000)	Utility weights from expert opinions. Estimations for different age groups.
Jassal et al 2003	QALY	Lifetime	3%	60 yr: 90,300/QALY (US$60,237) 65 yr: 101,600/QALY (US$67,779) 70 yr: 118,900/QALY (US$79,360) 75 yr: 149,200/QALY (US$99,553) 80 yr: 206,800/QALY (US$137,999) 85 yr: 346,500/QALY (US$231,158)	Only includes patients in good form. Results are affected by length of time on the waiting list. KTx is not cost-saving for the elderly.
Kaló et al 2001	Life-years	3 years	0%	Cost saving: 29,300 (US$18,290) per life-year gained	

LDKTx – living donor kidney transplantation; DDKTx – deceased donor kidney transplantation.

3.2 Liver transplantation

The literature search revealed six articles on the cost-effectiveness of liver transplantations (LTx) (Tables 2a-b) and four reviews (see appendix). In comparison to transplantation of other organs, liver transplantation is fairly well-studied, although there are still only a limited number of studies. The results indicate that LTx can be considered to be worth its costs, at least with deceased donors and for specific disease groups. More studies are required to establish the specific population subgroups for which LTx is cost-effective (based for example on underlying disease, health status, and underlying characteristics).

The economic evaluations described appear in general to be methodologically satisfactory. However, they all have some form of health care perspective and/or only include (direct) health care costs. It is thus difficult to assess the true value of liver transplantation to society, although it seems likely that LTx would be even more cost-effective when all societal costs and effects are accounted for. However, some of the studies do not even apply a full health care perspective, but rather the perspective of a specific clinic or centre. It is uncertain in these cases whether costs are shifted within the health care sector over time, and whether this then leads to an overestimate of the cost-effectiveness. More studies are needed, especially those using a societal perspective and including costs and benefits to all parts of society, before the actual value of the resources used can be established.

Living donor transplantation is considered in several of the evaluations, showing that in comparison to deceased donor transplantation, this procedure generally has a higher cost-effectiveness ratio and a higher ICER. However, it appears that it can also be cost-effective, especially when there is a long waiting list for an organ from a deceased donor. This is connected to the risk of complications and worsening health status during the time spent on the waiting list. When this risk of complication becomes sufficiently high, it outweighs the risk for the living donor. More studies are needed of living donor LTx, with a societal perspective and including all costs and effects, in order to determine the patient groups for which it has the potential to be most beneficial with respect to its costs.

Future economic evaluations of liver transplantations should especially endeavour to increase the follow-up period. The follow-up is relatively short in some of the published studies (e.g. Longworth et al (2003); Northup et al (2009)), especially when considering a societal perspective. In addition to this, it is also important that future studies should accurately capture the effect on living donors, again with a long follow-up period. This is lacking in prior studies, as the information has not been available (Sagmeister et al 2002). Finally, future studies also need to capture effects not related to the health care sector, for example the effect of transplantation on the probability of returning to the labour market, sickness absence, and the informal care provided by family and friends.

Table 2a. Economic evaluations of liver transplantations.

	Country	Year	N	Type of study	Approach	Perspective	Alternative
Majno et al 2000	NA	NA	NA	Markov model	Cost-effectiveness	Societal	Partial hepatectomy followed by salvage LTx.
Northup et al 2009	USA	2000-	NA	Markov model	Cost-utility	Health care/unit	Supportive care for decomposed end-stage liver disease.
Longworth et al 2003	England & Wales	1996-1999	208	Prospective /modelling	Cost-utility	Health care/unit	No transplant (gold standard)
Sagmeister et al 2002	Switzerland	1995-	NA	Modelling	Cost-utility	Societal	Natural history of disease (no transplant)
Ouwens et al 2003	The Netherlands	1978-1987	302 (81 LTx)	Retrospective	Cost-utility	Health care	No transplant (gold standard)
Ishida et al 2006	Japan	1999-2001	11/19	Prospective	Cost-utility	Societal (health care payer?)	Not stated (immediate death)

Table 2b. Economic evaluations of liver transplantations.

	Outcome	Follow-up	Discounting	Cost-effectiveness (US$)	Comments
Majno et al 2000	Life-years	Lifetime	3%	43,300 (US$27,932) per life-year gained	
Northup et al 2009	QALY	10 years	3%	DDLTx: 45,600/QALY (US$34,648) DDLTx with LDLTx: 57,200/QALY (US$43,487) ICER: 47,300 and 140,400 (US$ 35,976 and US$106,788)	
Longworth et al 2003	QALY	27 months	6% for costs 1.5% for outcomes	PBC: 68,200/QALY (£29,000) ALD: 112,800/QALY (£48,000) PSC: 49,400/QALY (£21,000)	Short follow-up and unit perspective.
Sagmeister et al 2002	QALY	Lifetime	3%	DDLTx: 38,000/QALY (€22,521) DDLTx with LDLTx: 38,400/QALY (€22,761) ICER 37,900 and 39,700 (€22,451 and €23,530)	
Ouwens et al 2003	QALY	Lifetime	Not stated	61,300/QALY (US$31,000)	Focus is on Tx; LTx only for comparison.
Ishida et al 2006	QALY	2 years	0%	LDLTx: 123,800/QALY (US$94,169)	Short follow-up. No clear alternative comparison. Does not account for costs in connection to the donor.

PBC – primary biliary cirrhosis; ALD – alcoholic liver disease; PSC – primary sclerosing cholangitis; DDLTx – deceased donor liver transplantation; LDLTx – living donor liver transplantation.

3.3 Lung transplantation

Few economic evaluations of lung transplantations (LuTx) have been performed in the last decade. The studies described in the appendix indicate that lung transplantation is probably cost-effective when compared to other medical treatments, see Tables 3a-b. However, they also suggest that the cost per QALY is higher than the standard US$50,000, although a large variation can be expected, depending on the underlying disease.

In general, these studies are well performed compared to some of the other transplantation areas. However, there are some problems with follow-up after transplantation, which is often short and thus requires extrapolation. Although this is due to data limitations, longer actual follow-ups are preferred. In addition, as some of the studies note, lung transplantation patients are not homogenous, and so estimates of cost-effectiveness must take patient and disease characteristics into account. There are also differences between the different lung transplantation procedures, as shown in Anyanwu et al (2002), and this should also be accounted for. Obviously, such subgroup analyses require a larger sample than is normally available in the field.

Table 3a. Economic evaluations of lung transplantations.

	Country	Year	N	Type of study	Approach	Perspective	Alternative
Groen et al 2004	The Netherlands	1991-1999	NA	Micro-simulation	Cost-effectiveness and cost-utility	Societal	No transplantation.
Vasiliadis et al 2005	Canada	1997-2001	124 (91 LuTx)	Cohort with retrospective data	Cost-effectiveness and cost-utility	Health care	No transplantation (waiting list).
Anyanwu et al 2002	UK	1995-1999	1030 (260SLuTx, 199 DULuTx, & 218 HLuTx)	Retrospective	Cost-effectiveness and cost-utility	Societal	Medical treatment (waiting list).
Ouwens et al 2003	The Netherlands	1992-1995	360 (57 LuTx)	Retrospective	Cost-utility	Health care	No transplantation.

SLuTx – single lung transplantation; DLuTx – double lung transplantation; HLuTx – simultaneous heart-lung transplantation.

Table 3b. Economic evaluations of lung transplantations.

	Outcome	Follow-up	Discounting	Cost-effectiveness (US$)	Comments
Groen et al 2004	Life-years & QALY	25 years (lifetime)	5%	108,300 – 222,800 per life-year (US$75,200-154,700) 110,900 – 129,500 per QALY (US$77,000-89,900)	Estimation of the cost-effectiveness of transplantation for seven different diseases.
Vasiliadis et al 2005	Life-years & QALY	5-58 months (+ extrapolation)	5%	55,100/life-year (US$40 048) 64,200/QALY (US$46 631)	Short follow-up, which requires extrapolation.
Anyanwu et al 2002	Life-years & QALY	Up to 4 years (+ extrapolation)	6%	Per life-year: SLuTx: 76,200 (US$50,825), DLuTx 68,000 (US$45,393), HLuTx 62,500 (US$41,720) Per QALY: SLuTx 72,300 (US$48,241), DLuTx 49,200 (US$32,803), HLuTx 43,900 (US$29,285)	
Ouwens et al 2003	QALY	Lifetime	Not stated	118,600/QALY (US$60,000)	

SLuTx – single lung transplantation; DLuTx – double lung transplantation; HLuTx – simultaneous heart-lung transplantation.

3.4 Heart

There are relatively few economic evaluations of heart transplantation (HTx), and those that do exist have several limitations. The main limitation is that they only include a selection of the effects of heart transplantation. In addition, they were all performed from some form of health care perspective, and so do not include the wider costs and effects for the patient and others (e.g. labour productivity, informal care, etc.). It is therefore not possible to conclude anything about the value of heart transplantations to society. However, it appears that heart transplantations are within the normally accepted range for cost-effectiveness from the perspective of the health care sector, although it is obvious that more studies are required before this can be stated with confidence. Future studies need not only to capture more effects (on both the cost and the benefit side), but also to have a societal perspective and a methodology founded in health economic research.

Table 4a. Economic evaluations of heart transplantations.

	Country	Year	N	Type of study	Approach	Perspective	Alternative
Cope et al 2001	USA	1994-1999	268 (52 HTx)	Retrospective	Cost-minimisation	Health care/unit	Coronary bypass, mitral valve repair, and left ventricular reconstruction.
Dayton et al 2006	USA	1997-2004	95 paediatric HTx & re-Tx	Retrospective	Cost-utility	Health care/unit	No transplantation.
Ouwens et al 2003	The Netherlands	1984-1987	422 (76 HTx)	Retrospective	Cost-utility	Health care	No transplantation.

Table 4b. Economic evaluations of heart transplantations.

	Outcome	Follow-up	Discounting	Cost-effectiveness (US$)	Comments
Cope et al 2001	Short-term survival	Clinical follow-up	NA	123,500 (US$76,000) for HTx vs. 40,600 – 52,000 (US$25,000-32,000) for alternatives	Outcome measured only as survival at the clinic, i.e. very short-term.
Dayton et al 2006	QALY	Lifetime	3%	HTx: 60,600/QALY (US$50,000) Re-Tx: 106,600/QALY (US$88,000)	No costs or outcomes are assumed in the alternative due to high mortality.
Ouwens et al 2003	QALY	Lifetime	Not stated	88,900/QALY (US$45,000)	Focus on LTx; HTx only for comparison.

3.5 Pancreas

Pancreas transplantations (PTx) are generally performed in order to restore glucose control in diabetic patients with end-stage renal disease. In these cases, either the pancreas and kidney are transplanted simultaneously, or the kidney is transplanted first. The pancreas can also be transplanted alone, for diabetic patients without end-stage renal disease (Boudreau & Hodgson 2007). This review includes all of these transplantations.

The literature search found only one study published in the last 10 years that estimates a cost-effectiveness ratio following different types of pancreas transplantations. This study was included in the reviews by Boudreau & Hodgson (2007) and Demartines et al (2005). Thus, there are more reviews than actual economic evaluations of the cost-effectiveness of pancreas transplantation. The reviews described above are generally very cautious in their conclusions, mainly stressing the need for more and better economic evaluations in the field. Although Kiberd & Larson (2000) is a well-performed study, we must conclude that the cost-effectiveness of pancreas transplantation is uncertain, due to limited research. It is obvious that more economic evaluations should be performed, but they should also endeavour to include all costs and benefits, preferably from a societal perspective, and adhere to methodological requirements in health economic research.

3.6 Small bowel

Intestinal failure results in an inability to obtain the body's nutrient and fluid requirements by normal means. The standard treatment is intravenous nutrition (parenteral nutrition), although this can cause complications. Small bowel transplantation (SBTx) is aimed at restoring function in patients with intestinal failure (Ontario Medical Advisory Secretariat 2003). It should be considered for patients with irrevocable intestinal failure and complications of parenteral nutrition (Middleton & Jamieson 2005).

Intestinal transplantation is basically unstudied; our literature search revealed only one proper economic evaluation. Although this study is solid and addresses some methodological issues, it does not give any indication of the cost-effectiveness of small bowel transplantation (Longworth et al 2006). More studies are therefore needed, including all costs and benefits, preferably from a societal perspective.

4 Discussion and suggestions for future research

Earlier reviews have concluded that organ transplantations are cost-effective (Machnicki et al 2006) or within the range of other accepted medical interventions (Kreuger 1989). The basis for these conclusions is somewhat brought into question by the current review. The primary doubt stems from the fact that relatively few economic evaluations have been performed, given that several transplantation characteristics are expected to influence the cost-effectiveness. On the supply side, health care systems, organ procurements, and transplant procedures differ between countries, regions and even hospitals. On the demand side, patient and disease characteristics differ between studies, and as discussed are expected to influence cost-effectiveness estimations. This indicates that the area in general needs to be further studied. However, it may be stated with confidence that renal transplantation is a cost-effective and cost-saving treatment, compared to dialysis. Liver transplantation also appears to be cost-effective, although the basis for this conclusion is less steady than that for the case of renal transplantation. For all the other organ transplantation treatments discussed here, cost-effectiveness or cost-ineffectiveness cannot be established.

The effects and consequences of organ transplantations are much more thoroughly studied; survival, graft survival, quality of life, and costs have all been investigated in

various studies, mainly focusing on the health care sector/unit. However, as is evident from the literature review above, few studies of costs actually put costs and consequences together and conduct a proper economic evaluation. There are a few studies that consider a rudimentary cost concept in relation to some form of outcome, but these cannot be considered economic evaluations for several reasons, such as very limited cost categories, process outcomes, and no alternative for comparison. It should be noted here that there exist many economic evaluations of specific parts and procedures of transplantation, for example the use of different immunosuppressive medications (see e.g. Desmartines et al 2005). However, these do not establish whether the transplantation should be performed in the first place.

There are some problematic issues in the economic evaluations presented above. Firstly, most studies take some form of health care perspective. Although this is not a problem as such, it excludes several important societal aspects such as the cost to the patient, the cost to the patient's family and friends, and labour market outcomes (although this is sometimes assumed to be partly included in the QALY measure, see for example Kiberd & Larson 2000). A societal perspective is often preferred as it captures all effects on society, no matter who pays or benefits. In addition to the health care perspective, some of these studies were conducted from the perspective of a specific health care centre/unit. This further limits the usefulness of the results as, depending on the system, it is possible that costs are shifted within the health care sector. It should also be noted that in several cases where a societal perspective was used, not all of the relevant costs and benefits were included. In general, the perspective is often poorly handled in these studies.

Secondly, several of the prospective/retrospective studies use a limited follow-up period. A short follow-up period risks missing important effects of the transplantation compared to the alternative, such as future complications, but especially future benefits in the form of improved quality of life and productivity. The modelling studies generally do not have this problem, although these require much information on the long-term effects of transplantation in order to construct a good model. It is beyond the scope of the current article to review the details of the models.

Thirdly, patient and disease characteristics are expected to influence cost-effectiveness, and so it is important to conduct evaluations in different population subgroups (e.g. Studer et al 2004). Although most studies present sample characteristics, only a few estimate different cost-effectiveness ratios for different subgroups, including Longworth et al (2003) for three different diseases and Jassal et al (2003) for age and co-morbidity. This limitation in earlier studies is probably due to a low number of transplantations being performed, which limits the sample and thus renders subgroup estimations insecure. However, the number of transplantations has increased in recent decades and future studies should conduct subgroup analyses if possible, including age and gender analyses as well as division by disease.

Fourthly, there is the issue of sample selection. As discussed above, randomised controlled studies are problematic, and so the transplantation sample is generally not comparable to those remaining on the waiting list or receiving standard non-transplant treatment. An example of this is renal transplantation compared to dialysis, where the former group has been shown to be younger and have less co-morbidity (Kontodimopoulos & Niakas 2008). This hinders the comparison between the effects of transplantation and the effects of standard non-transplantation. It should also be noted that several of the economic evaluations included in this review do not use appropriate comparison alternatives. In several cases, the alternative is assumed to be a situation with immediate death, and hence no incurred costs or benefits. This is not reasonable, as all patients receive supportive care at the very least. One way around this, used in several of

the studies, is the modelling approach. This, however, requires extensive information on the effects of disease and treatment. Extreme differences between the modelling and prospective/retrospective approaches, as demonstrated in Longworth et al (2006), need to be explained before the potential advantage of modelling can be established in cost-effectiveness studies of organ transplantations. Natural experiments, if any can be found, may offer another way to account for this problem.

Another side of this problem is that even if several treatment alternatives exist, the individual patient might not be eligible for more than one. This bias in sample selection will obviously render appropriate comparisons of (incremental) cost-effectiveness ratios difficult. One suggested solution is to evaluate not treatment alternatives but rather full programmes of, for example, end-stage renal disease (Wingelmayer et al 2002). However, another issue that complicates the matter is that the quality of care might differ between hospitals. It has been shown that high quality care is associated with lower future costs due to reduced complications, and vice versa (Englesbe et al 2009).

Fifthly, several of the studies report only limited information, which hinders evaluation of their methods and results. For example, it is difficult, in general, to assess whether relevant opportunity costs have been used rather than charges or expenditures. Lacking or unclear information also makes it difficult to interpret the perspectives of the studies and understand what is controlled for in the alternatives in the incremental analyses.

A final issue worth mentioning is the focus on "successful transplantations" in several of the evaluations. It is often unclear whether the effects of unsuccessful transplantations are included in the cost-effectiveness ratio. Obviously, it comes as no surprise that most successful medical treatments are cost-effective, while unsuccessful transplantations are not. It is not clear whether this is a real problem or just an effect of vague wording in the studies.

It would be possible to go into more depth in discussing the methods used in the studies above. However, this would be of limited value, as what are most urgently needed now are more studies in order to establish a sufficient base for such discussion. We will therefore now turn to some tangible suggestions for future studies.

Based on the results of this literature review, we recommend that future economic evaluations of organ transplantations should be performed from a societal perspective, considering differences in patient and disease factors, and making comparison to a relevant (actual) treatment option without transplantation. Rich datasets should be utilised, allowing follow-up in non-medical aspects such as labour market outcome (unemployment, sickness absence, early retirement, etc.) as well as health care utilisation. Possible effects on the living donor must also be captured in future studies, preferably over a long time period. It is also important to conduct country-specific evaluations, as generalisation of international results is difficult (Anyanwu et al 2002). On that note should future studies also endeavour to conduct appropriate sensitivity analyses in order to establish the robustness of the results. This is often lacking in recent studies, making both conclusions of cost-effectiveness and generalisation of results difficult.

Economic evaluations of all types of transplantations are needed, especially those analysing specific patient groups, but the need for more studies is largest for heart, lung, bowel, and pancreas transplantations. As established above, liver and kidney transplantations are relatively well-studied and their general cost-effectiveness has been established. Pancreas transplantation is especially interesting, given the high incidence of diabetes in many areas of the world, although the future focus might rather be on islet of Langerhans transplantation. Future projects should be defined and planned in

collaboration between the health economic field and the medical profession, in order to ensure high-quality studies.

Finally, we recommend that future studies should look into methods to reduce estimation bias in observational data, due to non-comparable samples in the alternatives. Matching for age, gender, and disease could be a first step, but more advanced statistical matching methods should also be tried, such as propensity score matching.

5 Conclusion

In this article, we have reviewed the available literature on the cost-effectiveness of organ transplantation, published since 2000. With the exception of kidney and liver transplantation, very few studies exist, making it impossible to establish cost-effectiveness. For the kidney and liver, indications are that transplantation is cost-effective. Future studies should endeavour to expand on existing studies by taking a societal perspective, including more costs and benefits, increasing the follow-up period, and comparing to relevant treatment alternatives. If possible, analysis in relevant population subgroups should also be performed.

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