Author's response to reviews

Title: A critique on the Policy Statement of the American Academy of Pediatrics - Children as Hematopoietic Stem Cell Donors - conditions too easy to fulfill

Authors:

Theo K Chan (theo@hku.hk)
George Tipoe (tgeorge@hkucc.hku.hk)

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Author's response to reviews: see over
Editors
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Dear Editors,

Re: A critique on the Policy Statement of the American Academy of Pediatrics
- Children as Hematopoietic Stem Cell Donors – conditions too easy to fulfill

I realised that my original article is full of mistakes after I read the comments from the reviewers. I am truly indebted to their valuable time and tremendous effort in pointing out the various issues that I have to address.

I would first like to invite you to read the following revised abstract to refresh your memory about my manuscript.

Revised abstract of the manuscript

Background
With a view to addressing our moral concerns about the use of donor siblings, the Policy Statement of the American Academy of Pediatrics - Children as Hematopoietic Stem Cell Donors (the Policy) has laid out the conditions upon which tissue harvest from a minor would be morally permissible.

Discussion
Although tissue harvest serves the best interests of recipient siblings, parents are also obliged to act in the best interests of the donor sibling. Parents should be forbidden, and they are by law, to consent to tissue harvest if the potential harm for an incompetent minor donor outweighs the possible benefits. Although we do require that people do no harm to others, there is no basis we morally or legally oblige a potential donor to save the lives of another individual unless it serves the best interests of the donor to do so. Tissue harvest should proceed if and only if it serves the best interests of both the donor and recipient. While fulfilling the conditions specified in the Policy alone is not sufficient to justify tissue harvest from a donor sibling, the legitimacy of tissue harvest should depend upon the availability of other types of donors and the type of disease.

Summary
Unless a recipient sibling will suffer from serious complications or die without the transplantation and no unrelated donors or related haploidentical donors are available, there is no moral or legal basis to violate the donor sibling’s right to bodily integrity. In short, the Policy fails to address our ethical concerns in relation to tissue harvest from donor siblings, and therefore ought to be revisited and revised accordingly.
A brief summary of the major revisions

Before I address the individual points the reviewers have raised, I would like to briefly describe the major revisions that I have made to the original manuscript.

In the original article, I restricted my discussion to the use of ‘saviour’ siblings. But in the revised version, my discussion applies to all donor siblings in general.

In the original article, I considered that a balance of the best interests of the donor sibling should underpin the ethical evaluation of tissue harvest. But in the revised version, I considered that parents are also obliged to act in the best interests of the donor sibling and that parents should be morally forbidden, and they are by law, to consent to tissue harvest if the potential harm for an incompetent minor donor outweighs the possible benefits.

In the original article I proposed that tissue harvest would be legitimate only if it is impossible to preserve the life of the recipient without the transplantation. Now I have revised my position and suggested that the following condition should replace the third condition in the policy:

3. The recipient sibling will likely suffer from serious complications or die without transplantation before the donor sibling becomes Gillick competent,

and that the following additional condition should be added:

6. Unless transplant involves only umbilical cord blood without modified delivery, physicians should make sure that, transplant from tissue-matched unrelated donors or haploidentical donors cannot offer a similar chance of survival and risks of complications for the recipient or that there are no suitable tissue-matched unrelated or haploidentical donors, if the medical conditions of the recipient permit a search.

(see page 10 – 11 of the revised manuscript)

In the revised article, I put forward a new argument that whereas the advantages of tissue harvest for donor siblings are long-term and merely psychological, the other side of balance sheet consists of short-term psychological burden and life-threatening physical harm. While there is no long-term psychosocial harm for the donors, they can reap significant long-term psychosocial benefits only if no other source of donation could have likely saved the lives of the recipient siblings.

(see page 7 – 8 of the revised manuscript)

Last but not least, I have also responded to each of the individual comments from the three reviewers as follows:

Responses to individual comments from Dr Joerg Halter

Comment 1
Risk-benefit assessment: In the risk-benefit assessment for the “saviour” potential psychological harm is mentioned under the title well-documented risks. As the authors conclude by themselves in the next two sentences it is unclear if this harm is real. Therefore this issue should be mentioned in a separate chapter “speculative risks”.

My response:
I agree. I have removed the discussion of psychological effect under the subheading ‘well documented risks’.

Comment 2

The role of an independent donor advocate should be introduced and discussed

My response:
I would like to focus on the principles of ethical evaluation of the best interests of the donors in this article rather than who should be responsible for taking up the duty. Furthermore, the concept of donor advocates is not be applicable in the UK and some states of the US.

Comment 3

I am not sure if the court case Re A really meets the point in this situation as it is also discussed by the authors in the next section.

My response:
I agree. I have removed the reference to the case Re A.

Comment 4

The chance to survive with transplantation is highly variable depending on the diagnosis, disease status (which is among other factors also time-dependent) and the type of transplantation (HLA-identity, stem cell source, etc.), i.e. there is never a 100% guarantee for success - or failure.

My response:
I did not require that success of transplantation has to be guaranteed as a condition of tissue harvest.

Comment 5
******
For many diseases there is also a chance to survive without transplantation but this chance is usually very much lower.
******

My response:
I agree. I suggested modification of condition 3 as a result.

3. The recipient sibling will likely suffer from serious complications or die without transplantation before the donor sibling becomes Gillick competent.

Comment 6
******
For most patients a transplant could be performed with an adult haploidentical donor, for many patients with a cord blood transplantation or with an unrelated donor. However, in many situations results are inferior compared with a HLA-identical related donor transplantation.
******

My response:
I agree. But I also bear in mind that new regimens of transplantation using unrelated and/or haploidentical donors have been developed with similar efficacy and safety compared with tissue harvest from tissue matched siblings.

In the premises, I suggested addition of condition 6 such that tissue harvest would be permissible if transplant from tissue-matched unrelated donors or haploidentical donors cannot offer a similar chance of survival and risks of complications for the recipient.

Comment 7
******
the most important question—which is not addressed by the authors yet would be: who makes the final decision? This should not be the parents or the treating physicians of the patient.
******

I prefer not to discuss who should make the final decisions because I am concerned with the ethical and legal principles only. Indeed, regardless of whether it is the parents or the physicians or the donor advocate who makes the decision, so far as the case satisfies the revised six conditions, I am convinced that the donor can be protected sufficiently. I do not think that the parents or physician cannot make the decision. The most important matter is that the decision maker follows the correct principles. So far as there is a system to scrutinize the process of decision making,
donor advocates are not essential and parents/physicians should be allowed to make a
decision. Different systems may serve the same purpose of scrutinisation. Of course,
the use of donor advocates is good but it is not with problems as parents may
complain that they are deprived of the parental right to make decision for their
children. In the UK, where parents and/or physician make the final decision, the court
still has the final say when dispute arises.

Comment 8
*****
the suggested circumstances are not feasible in daily
practice, the final conclusion from the author’s statement for daily practice would
be that no pediatric donors should be allowed to donate.
*****

My response:
I agree. I have revised my conclusions accordingly.

Responses to individual comments from Dr Elaine Morgan

Comment 1
*****
The authors cite John Stuart Mill stating the “the only purpose for which
power…..
The implication of this citation is that the “savior” is being forced to donate
against his/her will. There needs to be discussion of the meaning of “will” in a
young child and the data that support that these “donors” would indeed refuse to
donate if they could make such a determination. The other issue here is who
determines what the will of these young children is,*****

My response:
I was referring to the will of the parents. I apologise for the confusion and the revised
version should have made this clear. (see page 5 of the manuscript)

Comment 2
*****
The authors speak about the risks of general anesthesia and CVL placement.
There is data on the level of risk which should be included. The percent of bad
events needs to be compared to the percent risk encountered by a child in day to
day life to understand the degree to which the donor is at risk.*****

My response:
I agree. It has been incorporated. (see page 6 of the manuscript)
Comment 3

*****
The authors speak about the uncertainty as to whether the siblings will remain close. This assumes that the altruistic benefit is entirely dependent on future closeness rather than initial relationship. One may feel a filial responsibility whether or not the siblings remain close.
*****

My response:
I agree. In my revised article, the benefit of having the companion of a healthy sibling is no longer dependent on future closeness. But the sense of pride (one of the long term benefits) may not materialize if the grown-up donor sibling does not accept the filial or social responsibility to save the recipient sibling.

Comment 4

*****
It is stated that the sibling’s survival will reduce the amount of free time the parents have for the donor. By this argument parents should not have second children (or more) since a priori a new infant will dilute the individual attention. Furthermore a sibling who develops chronic illness related to chronic GVHD (more likely from an unrelated donor) or who is ill with progressive disease and/or who dies will also reduce the amount of free time of the parents.
*****

My response:
I agree. This argument has been removed.

Comment 5

*****
The “savior might be subject to blame. However, equally the “savior” might be subject to blame for not being the donor.
*****

My response:
I agree. This argument has been removed.

Comment 6

*****
The authors argue that the medical risks of harvest violate a “saviour’s right” to bodily integrity. The same could be said of vaccination and other medical procedures where the benefit is potential and never guaranteed. We grant parents the right to make these decisions for their children since the parents are assumed to be the best surrogate and have the responsibility to make these decisions for their children.
*****
My response:
I agree. My revised manuscript emphasized more the balance of risks and benefits.

Comment 7

******
The authors state that it is worthwhile to take risks only if benefits are well proven. But many medical treatments associated with risk are undertaken for children for the potential but not guaranteed benefit. One would better argue that risks are worth taking if the potential benefit is equal to or greater than the risk.

******

My response:

I agree. In my revised manuscript, I stressed that the notion of benefits and risks are both relative concepts. To consider the potential gains or losses for donor siblings, we ought to consider what would likely happen to the donors and recipients without tissue harvest. As all donor siblings reporting predominantly positive psychosocial experience in Macleod’s study had successful transplant, we contend that the long-term psychological benefits for donor siblings mainly derived from the survival of the recipient sibling rather than from tissue harvest per se. If a recipient sibling can survive without serious complications through donation from an unrelated or haploidentical related donor then tissue harvest may not offer any additional significant long-term benefits for the tissue-matched donor sibling.

As a result, whereas the advantages of tissue harvest for donor siblings are long-term and merely psychological, the other side of balance sheet consists of short-term psychological burden and life-threatening physical harm. While there is no long-term psychosocial harm for the donors, they can reap significant long-term psychosocial benefits only if no other source of donation could have likely saved the lives of the recipient siblings. Therefore, it is in the best interests of a donor sibling for tissue harvest to take place only if there are no other available donors who can offer the recipient sibling a similar chance of survival and risks of complications.

Comment 8

******

In Re A. This case is used to illustrate the “least detrimental choice. However, the relevance to the “savior” donor is questionable since in the case of In Re A, there could be benefit to only one of the conjoined twins, whereas in the case of a sibling donor, there is at least potential benefit to both children.

******

I agree. I have removed discussion of the case Re A.

Comment 9
The authors query whether there is another alternative transplant. However, they fail to consider the increased risk of such a transplant including delay, higher risk of non-engraftment and of chronic GVHD. This argument should consider the increase risk of physical harm, emotional stress to the patient and family and financial costs related to the increased medical complexity. Thus the balance is not simply life and death but must consider the associated medical and nonmedical costs of the proposed type of transplant.

My response:

I agree. In my revised manuscript, I consider that parents and physicians should make sure that no other sources of equally or similarly effective transplant are available before subjecting a minor to the physical risks and short-term psychological harm of tissue harvest. This is because new regimens of transplantation using unrelated and/or haploidentical donors have been developed with similar efficacy and safety compared with tissue harvest from tissue-matched siblings. Of course the non medical costs of the proposed alternative transplant such as delay have to be considered. Therefore, the sixth condition I propose is as follows:

‘Unless transplant involves only umbilical cord blood without modified delivery, physicians should make sure that, transplant from tissue-matched unrelated donors or haploidentical donors cannot offer a similar chance of survival and risks of complications for the recipient or that there are no suitable tissue-matched unrelated or haploidentical donors, if the medical conditions of the recipient permit a search.’

The underlined condition is a sufficient safeguard because if the family cannot afford the alternative transplant, then the medical conditions of the recipient will not permit the search.

Comment 10

the authors do not make any statement about at what age an “altruistic donation” can reasonably be made.

My response:
I agree. I have added the following statement:
‘Tissue harvest would be morally and legally acceptable if a donor sibling is Gillick competent and chooses to save the life of a sibling despite the risks.’ (See page 5 of the manuscript).

Comment 11
The authors refer to the Children’s Act of 1989. They correctly state that the child’s welfare is the court’s paramount consideration. While this is correct, the act primarily addresses custody and placement of needy children and does not state that the court can decide.

My response:

The court can decide whether a medical treatment is in the best interest of the child. See the case Re C & F (Children) 2003 EWHC 1376 (Fam), and Re C (HIV Test) 1999 2 FLR 1004.

Comment 12

The authors refer to In Re C(HIV test). Again the relevance of this decision to the current discussion is questionable. In In Re C the parents refused HIV testing based on personal beliefs with obvious and substantial harm to the child. This was disallowed on the basis that the child’s welfare was paramount. This argument is correct. However, this case is more relevant to a situation of refusal of standard medical care than a discussion of who can make a decision about a sibling marrow donation.

My response:
I agree. I have removed discussion of Re C(HIV test)

Comment 13

The authors refer to In Re C(HIV test). Again the relevance of this decision to the current discussion is questionable. In In Re C the parents refused HIV testing based on personal beliefs with obvious and substantial harm to the child. This was disallowed on the basis that the child’s welfare was paramount. This argument is correct. However, this case is more relevant to a situation of refusal of standard medical care than a discussion of who can make a decision about a sibling marrow donation.

My response:
I agree. I have removed discussion of Re C(HIV test)

Comment 14

The authors state that but for “the benefits of the sick sibling in the first place it would be unlawful to subject the savior to…. And the court would not sanction the transplantation taking place save in the most extenuating circumstances.”
However, the parents are motivated to allow the donation for the same reasons and would certainly not be allowing a donation if not for the sick child. The court therefore is not differing in this from the decision of reasonable parents. Further comment would be very welcome.

*****

My response:

I agree. I have removed this statement already.

Comment 15

*****

The authors exclude umbilical cord donations from the algorithm since there is no medical risk. However, arguably the risk of loss of parental attention and emotional risks (guilt) of the donor child would in fact not be different from any other type of marrow donation.

*****

My response:

I have removed discussion of ‘parental attention’. For umbilical cord blood harvest without modified delivery, there is no short term medical risks or immediate psychological harm involved. As I argued in the revise manuscript the donors will not suffer long term psychological harm because ‘negative psychosocial effects are more likely associated with the poor outcome for the recipient than due to the harvest per se. The donor would likely have suffered from the same psychological harm subsequent to the loss of a sibling even had the transplantation not taken place.’ In view of absence of risks I do not object to umbilical cord blood harvest even if the case does not satisfy the newly added condition 6.

Comment 16

*****

As to the “speculative” benefits, we all make decisions for ourselves and our dependent children based on “speculative” benefits.

*****

My response:

I agree. I no longer distinguish benefits and risks as being ‘speculative’ or definite.

Comment 17

*****

The authors distinguish between “savior” and donor based on the inability of the child to make an altruistic donation.

*****

My response:

I agree. I no longer distinguish saviors and donors, whereas my revised arguments apply to tissue harvest from donor siblings in general.
Comment 18
*****
the authors could perhaps augment the discussion of altruism by looking at what the majority of siblings who are competent to decide do in the parallel situation
*****
My response:
Siblings who are competent can decide to donate tissues based on factors which only competent persons can weigh. I consider that the decision for incompetent minors should only be based on the assessment of their best interests. The decision of the majority of competent siblings is not a factor that we should consider when we determine the best interests of incompetent minors. For instance, competent siblings may relish in the sense of pride of donating and consider this a huge psychosocial benefit. But in an objective assessment of a minor donor’s best interests, unless a recipient sibling will likely suffer from serious complications or die without the transplantation and no unrelated donors or related haploidentical donors are available, there is no significant long term psychosocial benefits that minors can accrue.

Comment 19
*****
I believe they fail to consider the question of whether the decision should rest of whether there is ANY alternative treatment versus the question of optimal medical treatment as not all transplants are equally beneficial or relatively safe.
*****
My response:
I agree. In my revised manuscript, I submit that tissue harvest would be permissible if there is no available alternative treatment which is similarly effective and safe.

Responses to individual comments from Dr Heidi Mertes

Comment 1
*****
Whereas the Policy Statement deals with children as HSC donors in general, this manuscript only considers so-called saviour siblings.
*****
My response:
I agree. I have revised the manuscript in such a way that the arguments apply to all donor siblings in general.

Comment 2
*****
The authors should elaborate on their own two additional criteria.

*****

My response:

I agree. I have indeed revised the suggested modifications and they are well elaborated. There is no more use of the term ‘invariably’ or ‘impossible’. And a search of other types of donors needs to be done only if the medical conditions of the recipient permit a search.

Comment 3

*****

Please quote the Academy’s statement correctly: not ‘some’ likelihood that the recipient will benefit, but ‘a reasonable’ likelihood. *****

My response:
I have checked and confirmed that my quotation of the statement is correct. (see http://pediatrics.aappublications.org/content/125/2/392.full)

Comment 4

*****

Although the parents’ wishes should command very great respect, the court (in our case, the parents) is to exercise an independent and objective judgment.”

*****

My response:
I agree. The confusing phrase ‘in our case, the parent’ has been removed.

Comment 5

******

However, the Academy also mentions that a sibling gives better chances of survival and that searching the registry implies losing valuable time and is sometimes not affordable by the parents. These additional arguments should at least be mentioned. ******

My response:
I agree. Though in my revised manuscript I advise a search for tissue matched unrelated donors and haploidentical related donors if such alternative transplantation can offer similar efficacy and safety, I stress this needs to be done if and only if the medical conditions of the recipient permits the search. (See my proposed modification to the policy on page 10 of the manuscript.)

Comment 6

******

“The issue at hand is to draw a line between our moral duty to protect the ‘saviour’ and to respect the right of the parents to make their autonomous choices”. Is the issue not rather to which extent a minor’s bodily integrity can be
harmed to save a life?

My response:
I agree. I have removed this statement.

Comment 7

The “recent useful court case” of separating two conjoined twins is not very persuasive.

My response:
I agree. Discussion of the case has been removed.

Further comment would be very welcome. I look forward to acceptance of my article soon.

Yours faithfully,

CHAN Tak Kwong