A view of paediatric outcomes research

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Costs of health care in the 21st century are on the increase. Whether delivering previously unavailable primary care to developing communities, treatment for resurgent malaria and tuberculosis in Africa, antiretrovirals for rampant HIV in the Third World, or newly developed technology and drugs to treat diseases of lifestyle and degeneration in affluent societies, health funding systems are having to decide on what is affordable. To make the necessary decisions one requires health economic data in the form of *cost-effectiveness* and/or *cost-utility* analyses.[1] The former provide information on the costs of achieving a clinical endpoint such as blood pressure reduction, whereas the latter typically inform on the costs per quality-adjusted life-year (QALY) gained.

By using QALYs one is able to assess clinical, economic and humanistic outcomes, and convert the results into a value that can be compared with other treatments for the same clinical situation, or even with other conditions altogether (Figs 1 and 2). One can, for example, look at the QALYs gained as a result of neonatal intensive care for 1 000 g babies and compare these with QALYs gained through placement of drug-eluting stents for the treatment of coronary artery disease, potentially enabling decision makers to rank one above the other when it comes to prioritisation of health care expenditure. This all sounds relatively simple and straightforward; however before we can ask whether we can *afford* what we are doing it is imperative that we know what we are actually *achieving* in various clinical situations.

There is usually a far greater demand for health economic information around complex, chronic and potentially costly problems than is the case for simple, short-term, inexpensive interventions, and one should therefore note that there are some very real issues in paediatrics. For example, and as shown in Figs 1 and 2, real costs in paediatrics extend way beyond the patient. Parents are involved to a greater or lesser extent, and depending on the chronicity and severity of the child's problem, employers may be affected through lost time and productivity. There may also be costs to society for institutional care and/or lost productivity on the part of the

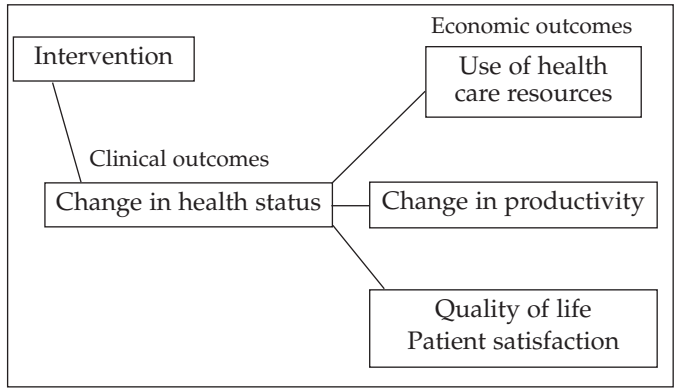

Fig. 1. Measuring value in health care.

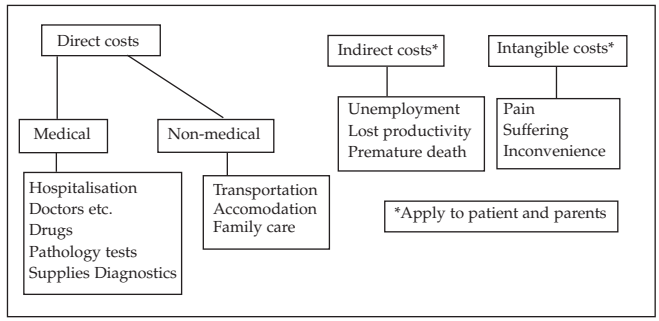

Fig. 2. Economic parameters in cost utility analyses.

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patient. As shown in a recent meta-analysis covering 150 paediatric health economic reviews, long-term costs and outcomes are typically measured extremely poorly, and parental impact is underestimated.[2]

'Scope of practice' is a limiting factor

Whereas in some cases adverse outcomes manifest soon after a clinical intervention (e.g. retinopathy of prematurity after oxygen exposure[3]) and it is relatively easy to abandon or modify the particular treatment, in other cases it takes years before unacceptable patterns emerge. Examples of the latter would be the development of gynaecological cancers in daughters of women treated with diethylstilbestrol (DES) during pregnancy,[4] or malignancy developing years after cervical irradiation as practised some decades ago for reduction of adenotonsillar hypertrophy.[5] The latter example is also important because it brings into play a particular problem in the field of paediatric outcomes research, i.e. the practitioner who diagnoses and treats the malignancy is unlikely to be the doctor who prescribed the original treatment.

This dissociation between the original and subsequent health care provider is aggravated in this country by so-called 'scope of practice'. While legislation confines specialist practice to each specialty or related specialties, the Health Professions Council of South Africa (HPCSA) is silent on age cut-offs for paediatrics;[6] however, conventions in both the private and public sectors have limited the extent to which paediatricians may continue to treat and follow up their patients. Medical schemes in particular apply restrictions and will often automate administrative processes to reject claims submitted by paediatricians for patients above a certain age (with different schemes applying different age cut-offs). The implication of the above is that experts in the field of congenital heart disease, paediatric renal disease, cystic fibrosis and other metabolic defects are systematically denied the opportunity to track long-term outcomes, while the patients themselves are subjected to follow-up by doctors who, by their own admission, are often not comfortable managing the original condition or its residual problems. Under such circumstances it is highly unlikely that reliable cost-utility analyses will emerge that will adequately cover all the costs and outcomes of more complex paediatric problems in the required manner.

The scope-of-practice restrictions as applied *between* disciplines can also be restrictive *within* the discipline of paediatrics as a result of subspecialisation. This means that the discontinuity of care found between paediatricians and physicians may also exist between specialist neonatologists and paediatricians. One also cannot ignore the fact that paediatricians lose contact with patients as a result of relocation, transfer to care by general practitioners or later on to care by specialists considered by the parents or patients to be more age appropriate. As a result of the above, horizons become even more limited, follow-up more difficult and, all too often, early survival becomes the only practical measure of outcome. Consequently, as with the DES experience, those who were involved in the initial care of patients may not see outcome patterns emerging and it may take time before harmful practices are modified or interventions abandoned.

Survival is a poor proxy for outcome in paediatrics

Neonatal surgery for complex problems represents an area in which long-term follow-up is obligatory, yet the paediatric literature abounds with reports that still only present survival figures. The question is always whether better survival statistics between units or after modifications to a procedure truly represent better outcomes. Management of congenital diaphragmatic hernia (CDH) is a case in point – here, poor survival after patient stabilisation with ECMO (extracorporeal membrane oxygenation)[7] was followed by a shift to less aggressive stabilisation of the affected neonate by means of 'permissive hypercapnoea'.[8] No one can dispute that survival statistics of ±75%[8] are much better than the 37% with ECMO,[7] but where are the data to show that neurodevelopmental outcome was not adversely affected by the prolonged hypercapnoea and moderate acidosis related to the intervention strategy?

Aggressive and creative cardiothoracic surgery for complex congenital heart diseases has also provided parents with hope of survival in previously hopeless situations, but this represents another difficult area in outcomes research because procedures are constantly being modified and it is difficult to equate outcomes after the original procedure with those achieved after three or four modifications. As with the CDH and ECMO example, survival of patients with hypoplastic ventricles may be considerably better after modifications to the likes of the Norwood and Fontan procedures,[9] but continued follow-up is required to confirm that the previously poor cardiac and neurodevelopmental outcomes[10] are improving to the same extent. Clearly what we need and are striving for in these difficult situations is a set of clinical guidelines that spell out 'best practice.'

What is 'best practice'?

Clinical guidelines are typically developed around what current evidence and opinion regard as the best way to manage a particular problem. In general one accepts that today's best practice might be replaced by a better alternative tomorrow, but there are also situations where best practice of the day has turned out to be harmful. Paediatric examples of this would be unrestricted oxygen therapy that was subsequently linked to retrolental fibroplasias,[3] or an early rotavirus vaccine that was later linked to intussusception.[11] These examples reinforce the

obligation of paediatricians to be vigilant when introducing new interventions, but it is equally important that we constantly monitor and evaluate accepted best practice and ask whether we are in fact achieving the best outcomes.

One paediatric situation that comes to mind with regard to monitoring accepted practice is the fairly standard use of unrestricted oxygen for neonatal resuscitation, and the general belief that short-term oxygen exposure is benign. This belief should perhaps be tempered by experimental and clinical evidence of hyperoxia-related reperfusion injury to the brain after asphyxia.[12] In spite of fairly extensive research that has supported their cause,[13,14] the proponents of air versus oxygen resuscitation have not been taken too seriously, perhaps because for most practitioners abnormal neurodevelopment after oxygen resuscitation would be attributed to the asphyxia and not the oxygen. However, it could also be that those who manage resuscitation units fear that withholding oxygen from newborns who do need it (because of lung disease) would be more harmful than providing it to those (with apnoea) who do not. Perhaps it is only a matter of time before this appears as a medicolegal issue with parents of a brain-damaged infant complaining that unrestricted oxygen was a contributing factor.

Another area in which best practice might be challenged is the management of small-for-gestational-age (SGA) neonates. The Barker hypothesis proposes that impaired intrauterine growth impacts on organs such as the pancreas and kidneys, setting the scene for cardiovascular and metabolic problems in adulthood.[15] Evidence suggests that accelerated early growth might be detrimental to such infants,[16] yet there is little that is more satisfying to most new parents and their chosen paediatricians than rapid weight gain in an infant born several hundred grams below the norm. Disciples of the Barker hypothesis are again in the minority, perhaps for the same reason as in the air versus oxygen debate – i.e. if too much is bad, what is the appropriate requirement for early weight gain? Should one aim to keep these SGA infants low on the growth charts or allow them to cross percentiles but at a slower pace? These questions, and the fact that the patient will be many years beyond the neonatologist's scope of practice if/when adverse consequences emerge, almost certainly mean that in this instance 'best practice' will continue as is. However, evidence is accumulating that might persuade paediatricians to become more accountable for changes that take place in adulthood.

An excellent role model for acceptance of long-term responsibility would be the Liggins Institute, which has committed to following up interventions such as the administration of steroids to mothers in preterm labour to stimulate surfactant production and prevent hyaline membrane disease in the infant. The original studies were done in the 1970s, and the 30-year follow-up has recently been published.[17] Results are reassuring in terms of clinical expression of cardiovascular disease in the offspring, but the metabolic studies confirm that changes have indeed taken place, and continued follow-up is therefore necessary to explore whether diabetes will be a problem in the future. Another example of long-term responsibility is the emergence of dedicated units for management of 'grown-ups with congenital heart disease' (GUCH units). These units are focused on continuity of care, recognising the need to engage paediatric and adult practitioners from clinical and psychosocial disciplines.[18,19]

Cynics might argue that best practice is a medicolegal concept and not a clinical one, serving as a defence for practitioners who did what most others were doing at a particular time rather than challenging them to evaluate individual and communal practices continuously to ensure that their interventions have indeed produced the best clinical, economic and humanistic outcomes. From a clinical perspective the term 'best practice' can confidently be applied only when we are certain that a patient's original problem has been fully treated by means of a specific intervention that has no broader effects. Ligation of an isolated patent ductus arteriosus can probably be regarded as definitive best practice while, as per the Liggins Institute example, one must consider that the jury is still out on the use of steroids for prevention of hyaline membrane disease. After all, in the latter situation one is using a potent hormone with diverse actions to achieve a specific result in an immature, developing organism. Under such circumstances how can one possibly be confident that there will not be any clinical spillover, and how can one do anything but commit to a programme of long-term observation?

No article on paediatric outcomes is complete without specific mention of follow-up of premature infants born at the limits of extrauterine viability. Suffice it to say that the administration of steroids as mentioned above is but one of several such interventions; however the requirement for follow-up is greater because these infants are even less mature at the time of exposure to potentially damaging agents and therapeutic modalities.

Conclusions

Paediatric outcomes research that includes QALY-type cost utility analyses is not only important from the point of view of affordability of interventions for the multitude of complex problems that occur during gestation or early in life, but it also provides insight into the quality of life and satisfaction of patients and their parents. This is a poorly developed area in paediatric practice and some reasons for the underdevelopment have been addressed in this review, together with some clinical examples. True and total care of children requires clinical audits, commitment to follow-up and intra- and interdisciplinary collaboration, paying attention to all relevant outcomes – clinical, economic and humanistic. Long-term

vigilance is necessary unless there is absolute certainty that an intervention has fulfilled all criteria for 'best practice' and an underlying problem has been treated with complete return to normality. Under other circumstances it is necessary to counsel parents, advise on appropriate preventive and promotive strategies and get their buy-in for the 'long haul.' External parties should not inhibit this process by introducing arbitrary scope-of-practice limitations, and medical schemes should be encouraging rather than obstructing follow-up where it is necessary.

References

1. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programs*. 2nd ed. Toronto: Oxford University Press, 1984.
2. Ungar WJ, Santos MT. Quality appraisal of pediatric health economic evaluations. *Int J Technol Assess Health Care* 2005; **21:** 203-210.
3. Locke JC. Retrolental fibroplasia: definitive role of oxygen administration in its etiology. *AMA Arch Ophthalmol* 1954; **51:** 73-79.
4. Hatch EE, Palmer JR, Titus-Ernstoff L, *et al*. Cancer risk in women exposed to diethylstilbestrol *in utero*. *JAMA* 1998; **280:** 630-634.
5. Yeh H, Matanoski GM, Wang NY, Sandler DP, Comstock GY. Cancer incidence after childhood nasopharyngeal radium irradiation: a follow-up study in Washington County, Maryland. *Am J Epidemiol* 2001; **153:** 749-756.
6. Department of Health. *Regulations Relating to the Specialities and Subspecialities in Medicine and Dentistry*. No. R.590. Pretoria: DOH, 2001. **www.hpcsa.co.za**
7. Davis PJ, Firmin RK, Manktelow B, *et al*. Long-term outcome following extracorporeal membrane oxygenation for congenital diaphragmatic hernia: the UK experience. *J Pediatr* 2004; **144:** 309-315.
8. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg* 2002; **37:** 357-366.
9. Azakie T, Merklinger SL, McCrindle BW, *et al*. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single institution experience. *Ann Thorac Surg* 2001; **72:** 1349-1353.
10. Forbess JM, Visconti KJ, Bellinger DC, Jonas RA. Neurodevelopmental outcomes in children after the Fontan operation. *Circulation* 2001; **104** (12 suppl 1), 1127-1132.
11. Bines JE. Rotavirus vaccines and intussusception risk. *Curr Opin Gastroenterol* 2005; **21:** 20-25.
12. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. *Semin Neonatol* 2000; **5:** 3-16.
13. Davis PG, Tan A, O'Donnell CP, Schulze A. Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet* 2004; **364:** 1329-1333.
14. Vento M, Asensi M, Sastre J, Lloret J, Garcia-Sala F, Vina J. Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr* 2003; **142:** 240-246.
15. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; **2:** 577-580.
16. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004; **363:** 1642-1645.
17. Dalziel SR, Walker NK, Parag V, *et al*. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005; **365:** 1856-1862.
18. Webb GD. Care of adults with congenital heart disease – a challenge for the new millennium. *Thorac Cardiovasc Surg* 2001; **49:** 30-34.
19. Somerville J. Management of adults with congenital heart disease: an increasing problem. *Annu Rev Med* 1997; **48:** 283-293.

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