Treating Children with Arthritis: Towards an Evidence-Based Culture

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ABSTRACT. We live in a culture of evidence-based medicine. Many areas of medicine have embraced this culture. However, for unusual diseases, like the childhood arthritides, there is little evidence. To provide this evidence a culture change must occur in pediatric rheumatology. The most convincing reason to make this change comes from the field of childhood oncology. Through successive clinical trials, collaborative oncology study groups have discovered cures for many childhood cancers. The most convincing studies are randomized trials; however, these are difficult to do. Collaborative trial groups and innovative designs are needed for an acceptable culture change in childhood arthritis. Recently a number of collaborations have been developed to help further the study of pediatric rheumatology. The best known are the Pediatric Rheumatology Collaborative Study Group in North America, and the Paediatric Rheumatology International Trials Organization in Europe, South America, and Asia. A new North American collaborative study group has formed – the Childhood Arthritis and Rheumatology Research Alliance (CARRA) – to undertake investigator-initiated clinical trials. These groups might potentially lead the way to a new evidence-based culture for childhood arthritis. (J Rheumatol 2005;32 Suppl 72:33-35)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
EVIDENCE BASED MEDICINE
RANDOMIZED CLINICAL TRIALS
TREATMENT

Until the 19th century it was supposed that the individual patient was so unique in his or her affliction that it was impossible to compare the experience of one to another. This changed when Pierre Louis introduced his so-called "numerical method." Louis counted up the number of deaths in patients with pneumonia treated with blood-letting, and compared that number to the mortality in similar patients who were not treated with blood-letting; he concluded that treatment with leeches led to more harm than good[1]. This was the beginning of a change in the culture of medicine.

We now live in the era of evidence-based medicine. Many areas of medicine have embraced this culture, and now patients (and their parents) expect to be treated according to the best evidence and research. However, for unusual diseases, like the childhood arthritides, few studies have been done to provide the rigorous evidence that is needed. In this article I will argue that in order to provide this evidence a culture change must occur in pediatric rheumatology.

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Dr. Feldman is supported by a Canada Research Chair.

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WHY CHANGE THE CULTURE?

Childhood arthritis is clearly an important problem. The various types of arthritis – collectively called juvenile idiopathic arthritis[2] – are about as common as other major chronic diseases of childhood like epilepsy and diabetes[3]. With modern treatments, deformities and disability are becoming less common[4], but childhood arthritis is chronic and painful; up to 60% of children will go into adulthood with active arthritis[5].

The most compelling imperative for culture change comes from the field of childhood oncology. Until the last half of the 20th century, childhood cancers – like acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, and Wilm's tumor – were almost uniformly fatal. Recognizing a great need for cure, as early as 1955, cancer treaters formed collaborative clinical trial groups like the Children's Cancer Group and the Pediatric Oncology Group (with the sponsorship of the US National Institutes of Health/National Cancer Institute). These groups have now merged to form the Children's Oncology Group (COG). Through successive clinical trials these groups have changed the culture of treatment of childhood cancer. The standard of care is now to treat all children with cancer on research protocols; the oncologists systematically learn from each new patient. The result is that in the 21st century these cancers are now largely curable.

According to the websites of the National Childhood Cancer Foundation (http://www.nccf.org/cog/about.asp) and the Children's Oncology Group (http://www.curesearch.org/aboutus/research/), nearly 90% of children with cancer in North America are treated according to COG protocols; currently over 40,000 children are being

treated. There are 235 COG member institutions and these are located in almost every North American state or province. Over 100,000 patients have participated in the member groups' studies over the last 30 years. The National Childhood Cancer Foundation convincingly argues that collaborative research has been the principal source of treatment advances and increased cure rates for childhood cancer over the past decades. The childhood cancer experience should be a strong incentive to similarly change the culture for treating childhood arthritis.

AN EVIDENCE-BASED CULTURE FOR CHILDHOOD ARTHRITIS?

One might ask why the treatment of childhood arthritis isn't evidence-based now? I don't believe that the problem has to do with a lack of desire or understanding on the part of the pediatric rheumatologists and allied healthcare providers who must treat these children, but rather, with a dearth of evidence: very few rigorous treatment studies have been done.

For treatment studies the gold standard is the randomized controlled trial (RCT). By allocating subjects randomly to the experimental and control treatment groups, we avoid selecting (consciously or unconsciously) those subjects who would have done better anyway, and placing them in the experimental treatment group. Also, by blinding the measurement of outcomes, we avoid seeing those in the experimental group as doing better when in fact they are not (or vice versa). Finally, through sample size planning and formal statistical analysis we can reduce the likelihood of a chance error. For these reasons the RCT avoids bias and gives us the best estimate of the effect of a new treatment.

However, there are problems with carrying out RCT. It is difficult to accrue subjects for any clinical trial – and this may be especially true for children. Parent acceptance of randomization (picking a treatment for their child in a process akin to flipping a coin) and blinding is often poor[6]. In some cases, pediatricians share these concerns[7]. A second problem is that RCT require lots of subjects to demonstrate moderate, but important, improvements in therapy. Large studies are very costly. If accrual is difficult, especially in an uncommon disease like childhood arthritis, RCT may not be feasible. As a result, there is very little available evidence upon which to base therapy for children with arthritis. When I searched Medline (OVID Medline, May 4, 2004) I found only 42 studies indexed under randomized controlled trials in the area of juvenile rheumatoid arthritis. Only 4 metaanalyses (formal summaries of evidence – the cornerstone of evidence-based medicine – are listed. Contrast this with the case of adult arthritis, in which there are 2288 papers indexed under RCT and 99 metaanalyses. (For heart disease I found 24,059 papers indexed under RCT and 1440 metaanalyses!) Clearly there is not much evidence available to guide those treating childhood arthritis.

STRATEGIES FOR CHANGING THE CULTURE

In general, when we want to study uncommon diseases, like childhood cancer or childhood arthritis, there are 2 basic strategies that we may use. First, we can attempt to increase the number of studied subjects. This can be done by increasing the acceptability of our protocols (to increase enrolment[8]), and by forming multicenter collaborations. Second, we can try to increase the amount of information we collect from each subject (in the sense of increasing the precision of the estimate)[9].

We already have the "raw materials" to implement these strategies. Over the last few years a number of collaborations have been developed to help further the study of pediatric rheumatology. The best-known groups are the Pediatric Rheumatology Collaborative Study Group in North America, and the Paediatric Rheumatology International Trials Organization in Europe, South America, and Asia. There are other groups as well, including the Canadian Pediatric Rheumatology Association, The British Paediatric Rheumatology Group, and the Paediatric Rheumatology European Society, all with an active role in research. Finally, a new North American collaborative study group has formed – the Childhood Arthritis and Rheumatology Research Alliance (CARRA) – in order to undertake investigator-initiated (rather than drug company sponsored) clinical trials. These groups might potentially lead the way to a new culture for childhood arthritis.

I suggest, as a first step, that we need to develop collaborative, multicenter clinical protocols that are acceptable to patients and physicians. In some cases these might be single-arm studies rather than RCT. The protocols must be simple; they should study a standardized treatment regimen using standardized data collection. Using adaptive analytic methods (for example Bayesian sequential studies[10]) we can design flexible studies that allow us to move on to study the "next" treatment once we have the answer to our current protocol. In this way we will change the culture; we will learn from each patient – in the way the cancer treaters have done for several decades – and work towards a cure for childhood arthritis.

There is a trade-off when we consider multicenter studies. Increased sample sizes and increased generalizability come at the cost of administrative difficulties and the potential for protocol degradation between the various sites.

In order to support a collaborative study group, therefore, a lot of infrastructure must be put into place. Multicenter protocols need a coordinating center. At this center there must be expertise in all aspects of running a clinical trial: experts in statistics, trial design, data management and case-report form design, and computer technology available to the investigators. Each participating center similarly needs infrastructure support. For example, busy clinicians need trial coordinators to make

sure that patients are being properly enrolled and studied. They need ways of communicating data (e.g., web-based data entry) and ways of communicating input into the design and conduct of these trials. This infrastructure is expensive. Funders need to step up and show a commitment to treating and curing childhood arthritis.

Based on the example of childhood cancer, a culture change seems necessary in order to find a cure for childhood arthritis. As treaters, we need to adjust our thinking; we will make the most gains if every child with arthritis is treated according to research protocols. This should become the standard of care. We will learn from each patient, and be able to provide an evidence base to allow for better and better care. It is hoped, with the support of national funding agencies, that we can work towards achieving the goal of a cure for childhood arthritis.

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