Evidence-based Pediatric Infectious Diseases

By

David Isaacs
Clinical Professor of Paediatric Infectious Diseases
University of Sydney and Senior Staff Physician
in Pediatric Infectious Diseases and Immunology
The Children's Hospital at Westmead
Sydney
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About the authors

David Isaacs is a senior staff physician in pediatric infectious diseases and immunology at The Children's Hospital at Westmead, Sydney, and Clinical Professor of Paediatric Infectious Diseases at the University of Sydney. He has published 10 books and over 200 peer-reviewed publications. His research interests are neonatal infections, respiratory virus infections, immunizations, and ethics. He has published also on medical ethics and several humorous articles. Professor Isaacs is on multiple national and international committees on infectious diseases and immunizations and is a reviewer for the Cochrane Collaboration.

Elizabeth Elliott is Professor of Paediatrics and Child Health, University of Sydney; Consultant Paediatrician, The Children's Hospital at Westmead; Director, Centre for Evidence Based Paediatrics, Gastroenterology and Nutrition; and Practitioner Fellow, National Health and Medical Research Council of Australia. She is Director of the Australian Paediatric Surveillance Unit and past Convenor of the International Network of Paediatric Surveillance Units. She is Senior Associate Editor and co-author of *Evidence Based Pediatrics and Child Health* (Moyer V, ed., BMJ Books 2000, 2nd edition, 2004).

Ruth Gilbert is Reader in Clinical Epidemiology at the Institute of Child Health, London, having completed her training in pediatrics. She has published extensively on the epidemiology of infectious diseases, both original papers and textbooks. She coordinates research programs on the evaluation of screening and diagnostic tests and treatment for congenital toxoplasmosis, and for neonatal group B streptococcal infection. She is coauthor of *Evidence-Based Pediatrics and Child Health*, by Moyer V et al. Ruth teaches evidence-based medicine, has published Cochrane reviews, and is a reviewer for the Cochrane Collaboration.

Michael E. Pichichero is Professor of Microbiology and Immunology, Pediatrics and Medicine at the University of Rochester in New York. He is board certified in pediatrics, in adult and pediatric allergy and immunology, and in pediatric infectious disease. Dr. Pichichero is a partner in the Elmwood Pediatric Group; a recipient of numerous awards, he has over 500 publications in infectious disease, immunology, and allergy. His major practice and research interests are in vaccine development, streptococcal infections, and otitis media.

Virginia Moyer is Professor of Pediatrics and Section Head, Academic General Pediatrics at Baylor College of Medicine and Texas Children's Hospital in Houston, Texas. Dr. Moyer has particular interests in teaching clinical epidemiology and studying the use of diagnostic tests in clinical care. She is a member of the Evidence-Based Medicine Working Group, the United States Preventive Services Task Force, and the International Advisory Board for the Cochrane Collaboration Child Health Field. She is Editor in Chief of the book *Evidence-Based Pediatrics and Child Health* (2nd edition), and the journal *Current Problems in Pediatrics and Adolescent Health Care*, and is a founding Associate Editor of *Evidence-Based Child Health: A Cochrane Review Journal*.

Preface

Some books provide comprehensive recommendations without giving the evidence. Some books provide comprehensive evidence without giving any recommendations.

There is a tension between providing useful management recommendations and between providing detailed evidence that allows clinicians to make their own decisions. Books on managing infections, like the excellent Antibiotic Guidelines[1] and the Red Book,[2] give recommendations about which antibiotics to use and the doses, but not the evidence supporting the recommendations. This is deliberate, to keep the books to a manageable length. In contrast, books such as that edited by Virginia Moyer[3] attempt to analyze the evidence for clinical decisions in depth. Sources of summarized evidence, such as the BMJ's important Clinical Evidence series, provide detailed evidence without recommendations and leave it to the busy clinician to weigh the evidence presented and decide about treatment. While helpful, the depth of the analysis of the evidence means that these sources can deal only with a limited number of clinical situations.

The fundamental principle of the current book is to combine the strengths of both approaches, by analyzing the evidence on management (treatment and, where relevant, diagnosis and prevention) if this is controversial or uncertain, presenting the evidence briefly and then our recommendations about management. The busy clinician can then weigh up the strength of the evidence for our recommendations, and decide how to act. Clinicians can also review the literature themselves, if they have time.

Evidence-based medicine (EBM) has great strengths. For years, many of us thought we were practising EBM, but the best evidence was not easily accessible. That has changed with increasing emphasis on randomized controlled trials, meta-analyses of randomized controlled trials, systematic reviews of the evidence and the rigorous approach to assessing the quality of randomized controlled trials included in the Cochrane reviews, and with the availability of electronic search engines to find the evidence.

Some have espoused EBM wholeheartedly and even, dare one say it, some have advocated it uncritically. It has been fun to satirize this overemphasis on EBM.[4,5] In reality, EBM has strengths and weaknesses. We should use its strengths while acknowledging its weaknesses.

When evidence is lacking, we still need to decide what to do with our patient. In infectious diseases, do we give antibiotics now or watch carefully? What about adjunctive therapy, steroids, or intravenous immunoglobulin, which might help in critical situations? Reading any of the spate of Practice Guidelines published recently is sobering, because so many of the recommendations are based on "consensus expert opinion" in the absence of good trial data.

In this book we present the evidence for management of many pediatric infectious diseases affecting children in industrialized and developing countries, travelers, and refugees. Our recommendations are based on current evidence about efficacy and safety, but also the likely effects on antibiotic resistance, the costs, adverse effects, ethical and any other relevant considerations.

David Isaacs

References

1 Therapeutic Guidelines Ltd. *Therapeutic Guidelines: Antibiotic*, 13th edn. Melbourne: Therapeutic Guidelines Ltd., 2006.

2 American Academy of Pediatrics. In: Pickering LK (ed.), *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2003.
3 Moyer VA, (ed). *Evidence-Based Pediatrics and Child Health*, 2nd edn. London: BMJ Books, 2004.
4 Isaacs D, Fitzgerald D. Seven alternatives to evidence-based medicine. *BMJ* 1999;319:1618.
5 Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327:1459–61.

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DI has been a member of the writing group for the book *Therapeutic Guidelines: Antibiotic* (TGA) from 1994, when the 8th edition was published until now, the 13th edition having been published in 2006. These books are the work of Therapeutic Guidelines Limited, a non-profit-making organization, which publishes evidence-based guideline books on many different areas of medicine. The first edition of TGA was published in 1978, and was the origin of Therapeutic Guidelines Limited. The aim of TGA, then and now, is to promote good antibiotic prescribing, which includes making recommendations that will minimize antibiotic resistance, and also, though less importantly, consider cost as a factor. A committee of experts, drawn from the fields of infectious diseases, microbiology, tropical medicine, general practice, and pharmacology, meets regularly to review the evidence and discuss treatment.

The recommendations in TGA focus almost entirely on antimicrobial use, rather than diagnosis or other aspects of management. While the book you are currently reading has considered the evidence independently of TGA, and also addresses diagnosis and adjunctive therapies, the presentation of antibiotic doses given in boxed format uses an almost identical format to that used by TGA, and we would like to acknowledge this. We have adopted this format, which has evolved over 28 years, because it expresses so clearly and unambiguously which antibiotics should be prescribed and how often. In addition, the actual pediatric doses we recommend are similar but not always identical to those used in TGA. DI would like to acknowledge his indebtedness to his colleagues on the TGA committees for their wisdom and experience, shared so selflessly. While hesitating to single out any one colleague, DI would like particularly to acknowledge Professor John Turnidge from Adelaide, for his advice on antibiotic use in children. DI would also like to acknowledge the staff of Therapeutic Guidelines Limited, notably Jonathan Dartnell and Jenny Johnstone for their expert support and assistance and Mary Hemming for her open support. Therapeutic Guidelines Limited has given permission for us to use their material to help direct our thinking and for us to include some of their antibiotic guidelines, and we gratefully acknowledge their generosity.

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Telephone: 613 9329 1566
Fax: 613 9326 5632
E-mail: sales@tg.com.au
Website: www.tg.com.au

Abbreviations

These abbreviations are used frequently in this book.

CI = Confidence Interval: a way of expressing uncertainty in measurements; the 95% CI tells you that 95% of the time the true value will lie within this range. For example, if you are told that a treatment compared with placebo has a relative risk of 0.50 (95% CI 0.31–0.72) that means the treatment reduces the risk by 50%, and 95% of the time it will reduce the risk by somewhere between 31 and 72%.

NNT = Number Needed to Treat: the number of patients you need to treat in order to achieve one extra favorable outcome. For example, if 9 of 10 patients treated with antibiotics for an infection get better compared with 7 of 10 treated with placebo, 2 extra patients get better for every 10 treated and so the NNT is 10/2 or 5.

OR = Odds Ratio: the ratio of the odds of having the outcome in the treated group compared to the odds of having it in the control group. For example:

- If 10 of 100 treated patients have persistent symptoms, the odds of persistent symptoms are 10/90 or 0.11 (11%).
- If 30 of 100 untreated/placebo patients in the same study have persistent symptoms, the odds are 30/70 or 0.43 (43%).
- The odds ratio is 0.11/0.43, which is 0.26.

RR = Relative Risk or Risk Ratio: the ratio of the risk in the treated group to the risk in the control group. For example:

- If 10 of 100 treated patients have persistent symptoms, the risk of persistent symptoms is 10/100 or 0.1 (10%).
- If 30 of 100 untreated/placebo patients in the same study have persistent symptoms, the risk is 30/100 or 0.3 (30%).
- The relative risk or risk ratio is 0.1/0.3, which is 0.33.

[When the event rate is 10% or lower, the OR and RR are similar. For more common events, the difference between OR and RR becomes wider, with the RR always closer to 1. In general, it is preferable to use RR.]

RCT = Randomized controlled trial: participants are randomly allocated to an experimental or control group and the outcome measured.

CHAPTER 1
Evidence-based practice

1.1 Why evidence-based practice?

We all like to think we are practicing medicine based on the best evidence available. However, we sometimes do things in medicine for one or more of the following reasons:

- "It has always been done that way"
- "Everyone does it that way"
- "The consultant says so"
- "The protocol says so"

We tend not to challenge the dogma because we are too busy or because we do not know how to find the evidence or because we think we know the evidence. If doctors are asked what are the main obstacles to them in trying to review the literature, the commonest answers are lack of time,[1–5] followed by lack of knowledge.[4,5] However, innovations have made it much easier and quicker to search the literature.

Sometimes the best evidence available for a clinical decision will be a high-quality systematic review of several good RCTs on patients like yours (see Section 1.5, p. 2). At other times, there may be no trials and the only evidence will be from observational studies, such as case series or even case reports. A clinician making the clinical decision will find it helpful to know the strength of the evidence and the degree of uncertainty in making that decision.

Young doctors should be encouraged to challenge dogma and to ask for the evidence supporting management whenever possible. Senior doctors should be quick to ask the young doctors to look it up themselves and return with the evidence. We should all be open-minded enough to accept that our current practices may be wrong and not supported by the evidence.

In the past our attempts to practice in an evidence-based way were hampered by difficulty in getting easy access to the evidence. Literature searches were cumbersome and evidence was rarely presented to us in a convenient or easily digestible way. That is no longer an excuse. Anyone with Internet access has immediate access to the best evidence and can review the recent literature in a few minutes.

The concept of evidence-based medicine (EBM) was developed by Sackett and colleagues at McMaster University in Canada during the 1980s and 1990s. They defined EBM as the integration of the best research evidence with clinical expertise and patient values.[6] Our ability to practice EBM has been enhanced by the development of systematic ways of reviewing the literature and the availability of search engines to find the evidence.

1.2 The Cochrane Library

The Cochrane Collaboration has revolutionized the way we look at evidence. The Cochrane Collaboration was founded in 1993 and named for the British epidemiologist Archie Cochrane. It is an international non-profit-making organization that produces systematic reviews (see Section 1.5, p. 2) of health-care interventions and makes sure they are updated regularly. We consider that a good Cochrane systematic review provides the best available evidence on interventions. This is because a Cochrane review involves a formalized process of finding all published and unpublished studies, assessing their quality, selecting only those studies that meet predetermined criteria, and performing a meta-analysis when possible. A meta-analysis is a way of combining the results from several studies to get an overall mathematical summary of the data.

Cochrane reviews are only about interventions, which often but not always involve treatment. Cochrane reviews on treatment usually include only RCTs because an RCT is the best study design for avoiding bias when assessing treatment. When considering the evidence for any intervention, it is almost always worth