

APPENDIX 3 LITERATURE REVIEW

Methods

Each chapter author used the specific expertise of the writing and review group and retrieved quoted articles from the 1999 document relevant to the chapter. Hand searches of important international and national journals were used in addition to standard reference sources such as PubMed and Cochrane Library. Each guideline in the 1999 document served as a template and was challenged in the light of updated data. As a result, a number of guidelines from 1999 were modified or replaced. A major concern of each group was to ensure the credibility, readability and the highest level of clinical relevance and application in the document.

Questions to be answered

The approach was to ask clinically relevant questions encountered in everyday practise and use the 1999 document as a template.

The chapters and sections have been developed in a sequence of clinical situations based on clinical questions developed using the PICO criteria (population, intervention, control and outcomes). Questions were developed by the subcommittee for each chapter and discussed when the Working Party met on 2 December 2003. There have been face-to-face and phone discussions since then.

Search methodology

The literature searched for each chapter is outlined below. The initial approach in each chapter was to review the references from the previous publication and update as appropriate. As a result of delays, a further review of Cochrane databases, PubMed, Ovid EBMR, Clinical Evidence and MD Consult were done as outlined between January 1998 and June 2004. Randomised control trials references were sent to writing groups except where otherwise specified. Hand searches have also been used.

Where a sound meta-analysis or a Cochrane review of relevant literature was available at the time of the search, it was cited in preference to quoting individual papers.

In 2004 (June), an updated review was done of the database outlined above. A hard copy of this standardised search including all references and, where available, abstracts were sent to chapter editors with a request that they critically evaluate each reference for relevance. If the reference was judged relevant and suitable, and not already incorporated, it was added to the references in the chapter and incorporated into the chapter text.

Some chapter authors were not sent this standardised search because they considered that the search they had already conducted was complete. In these cases the revision was made by the chapter chairs. Additional details of the methods followed for each individual chapter are outlined below.

If an author deviated from using the search, this is explained in the comprehensive explanation of the search strategy used for each chapter.

Chapter 1 — Setting the scene

This chapter provides a broad analysis of Colorectal Cancer in Australia and matters affecting clinical personnel, patients and carers. The literature quoted is eclectic, and chosen to highlight special patients to be addressed in the document.

Chapter 2 — Primary prevention and Chapter 3 — Population screening

Search strategy

A variety of sources were used:

- INGENTA reports from the Ingenta website, an online collection of academic journals and publications, were reviewed each week. These cover primary prevention of Colorectal Cancer, including chemoprevention and population screening
- daily reports on new publications produced by the Cancer Information Service at the Cancer Council of Victoria
- weekly reviews of new journals received by National Cancer Control Initiative (NCCI) and the Biomedical Sciences Library at the Royal Melbourne Hospital
- the Cochrane Library — visited regularly
- the literature database at the NCCI — the project officer in charge retrieved relevant literature

Selection of articles for consideration for the chapters depends on judgements about their reliability and contribution to the area. All articles about primary prevention using cancer or adenoma as an endpoint were considered for Chapter 2, as stated at the beginning of the chapter, with special emphasis on new approaches and results from large continuing studies. We have used articles published well into 2004.

Dates

Updated 1999 document to April 2004.

Search terms

Publications about primary prevention using cancer or adenoma as an endpoint.

Inclusion/exclusion criteria

Care was taken to include important reviews, for example, the *Handbook of cancer prevention* published by the International Agency for Research on Cancer (World Health Organization) in 2002, which reviewed weight control and physical activity; the Cochrane review on calcium supplementation; and the pooled analysis of eight cohort studies on alcohol intake and Colorectal Cancer, published in *Annals of Internal Medicine*, 20 April 2004.

Criteria for inclusion in the chapters were the timing of the publication (giving credit to original observations rather than confirmation, although several publications were often used to support individual statements), soundness of design, quality of the studies and relevance to the content of the chapters.

Results

Seventy-three new references were identified, increasing citations to 131, and 19 references were deleted from Chapter 2 of the 1999 document.

Comments

Special emphasis was placed on new approaches and on results from large ongoing studies. Many of the publications were focused too narrowly to warrant inclusion in the chapters.

Chapter 4 — Communication with the patient

Search strategy

Cochrane Library, PubMed/Medline, hand searches

Dates/limits

Updated 1999 document to June 2004

Search terms

Patient communications, cancer, surgery

Results

No Cochrane reviews were located.

PubMed and Medline databases revealed 819 articles, one meta-analysis and 16 randomised controlled trials.

Inclusion/exclusion criteria

Relevance to patient needs was the guiding factor.

Comments

The one meta-analysis and the great majority of retrieved articles were of little relevance as they were directed towards other cancers. New data were added from hand searching.

Chapter 5 — The patient with symptoms

Search strategy

Cochrane Library, PubMed/Medline

Dates

Updated 1999 document to September 2004.

Search terms

Rectal bleeding, Colorectal Cancer symptoms, colonoscopy, iron deficiency anaemia

Results

PubMed:

- meta-analyses for colonoscopy — 13
- RCTs for colonoscopy — 553
- RCTs for Colorectal Cancer symptoms — 507
- RCTs for iron deficiency anaemia — 74

Cochrane Library:

- systematic reviews Colorectal Cancer symptoms — 3
- RCTs for Colorectal Cancer symptoms — 6

Three Cochrane systematic reviews were not relevant to the chapter. Six Cochrane randomised controlled trials (RCTs) were evaluated, and one included.

Inclusion/exclusion criteria

Most publications were directed at screening, faecal occult blood testing, treatment regimes, anaesthesia, or diseases other than cancer. Those directed to non-procedural colonoscopy were carefully reviewed.

Comments

This chapter has been inserted to ensure that clinical notice is taken of risk factors for Colorectal Cancer and to ensure proper investigation of rectal bleeding.

Chapter 6 — Screening and family history and Chapter 7 — High-risk familial cancer syndromes

Search strategy/dates

The same process was followed as for Chapters 2 and 3. The original search was reviewed and updated by further search to June 2004.

Dates

Updated 1999 document to June 2004

Search terms

Chapter subsection headings

Inclusion/exclusion criteria

Official hereditary bowel cancer registers in Australia and New Zealand are annotated at the end of the chapter.

Authors used timing of publication, giving credit to original observations rather than papers confirming original observation. Several publications were often used to support individual statements. Other criteria were soundness of design, quality of the studies, and relevance to content of the chapter.

Results

Many of the publications focused on too narrow an area to warrant inclusion in the chapters.

Comments

As part of its development, Chapter 7 was reviewed by The Cancer Council Victoria Hereditary Bowel Group in July 2004.

Chapter 8 — Diagnostic tests and preoperative assessment

Search strategy

PubMed, Medline, English language publications

Dates

Updated 1999 document with search from 1998 to June 2004.

Search terms

Subsection titles from the 1999 chapter were used as search terms.

Inclusion/exclusion criteria

Relevance to diagnostic tests and preoperative assessments

Results

Four PubMed general papers. Remainder were on individual subjects.

Colonography (virtual colonoscopy) appeared as the most important update. *Section 8.1.5 Virtual colonoscopy* has been added.

Comments

Each article was discussed by the writing groups and, if relevant, included in the chapter.

A further meeting was held to review the current recommendations and decide whether change was necessary in view of the more recently published literature.

In general, there was very little change to the chapter, apart from the increasing role of colonography.

Chapter 9 — Management of epithelial polyps

Search strategy

Cochrane Library, PubMed

Dates

Updated 1999 document to September 2004

Search terms

Colorectal epithelial polyps, hyperplastic polyps, management, headings of sections in chapter

Inclusion/exclusion criteria

Citations required to address search terms, or be rejected

Results

Cochrane Library: seven references, one systematic review not relevant, three RCTs, two EBM, one clinical evidence

PubMed: seven RCTs — one included

Hyperplastic polyps: PubMed — 59 papers, no RCTs; Cochrane Library — no references; hand searching

Comments

Professor Finlay Macrae and Professor Jeremy Jass have a cutting-edge, running literature update and continuous engagement with the literature on this topic, active research insights, and Biennial Medline Reviews until September 2004.

Additions to the chapter are *Section 9.4.2 Other polyposis conditions* and *Section 9.5 Hyperplastic polyps and polyposis*.

Chapter 10 — Preparation for surgery

Search strategy

PubMed and Cochrane Library

Dates

1 January 1998 to June 2004

Search terms

Terms searched as per subheading titles of chapters with key words: stoma education and preparation (Section 10.2), bowel preparation (Section 10.3), blood transfusion and colorectal surgery (Section 10.4), thromboembolism prophylaxis and colorectal surgery (Section 10.5), antibiotic prophylaxis and colorectal surgery (Section 10.6).

Inclusion/exclusion criteria

Articles were excluded if they were not published in English; if found not to be relevant to the subject; if not relevant to Australian practices, for example, medication such as antibiotics not in routine use in Australia; if the full publication was not readily available either online or through library resources.

Results

Antibiotic prophylaxis and colorectal surgery (retrieved 29 articles — used one); thromboembolism prophylaxis and colorectal surgery (retrieved four articles — used 2); blood transfusion and colorectal surgery (retrieved 11 articles — used one); stomal related (116 RCTs, used one); bowel preparation (retrieved 175, used ten); body temperature (retrieved 22, used one); most studies applied to colonoscopy.

Comments

If a well conducted meta-analysis or Cochrane review of all relevant literature was available at time of search it was cited in preference to citing all the individual publications. A recent published meta-analysis was available and used to justify the changed guideline.

Chapter 11 — Elective surgery for colon cancer

Search strategy

English publications in PubMed and Cochrane Library

Dates

Update of 1999 document from 1998–2001, subsequently updated to June 2004.

Search terms

Colon cancer, surgery, key words from subsection of chapters

Inclusion/exclusion criteria

Clinical importance, shift in surgical thinking

Results

There are 42 references in Chapter 11. Of these, 17 were included in the original guidelines, and 19 new references and one personal communication were identified in the initial search as follows:

- one meta-analysis (ref 8)
- seven randomised trials (25, 26, 27, 29, 30, 31 and 32)
- three represented a shift in surgical thinking (6, 21, 24)

- seven were papers on new subjects: refs 9, 10, 11 on omental wrapping of anastomoses; refs 34, 35, 36, 37 on metal stents for obstructing cancer
- one paper — the most up to date Australian paper on a subject where no local paper has been published (ref 28)
- one personal communication from the coordinator of the Australian randomised trial comparing open and laparoscopic colectomy — the work is unpublished as the trial is not complete.

In a further literature review in June 2004, a review of the Cochrane Library revealed eight randomised controlled studies. These were considered, but did not add substantially to the manuscript as five included chemotherapeutic approaches (Chapter 15), one referred to antibiotic and chemoprevention of wound infection (Chapter 10), and one to surgical volume and outcome (Chapter 12). References 33, 34 and 35 were added to Section 11.11, stressing the current status of laparoscopic colectomy.

Chapter 12 — Elective surgery for rectal cancer

Search strategy

PubMed, Ovid and Cochrane Library

Dates

Updated 1999 document from 1980 to 2002, and further updated to June 2004

Search terms

Rectal, rectal cancer, surgery

Inclusion/exclusion criteria

Clinical importance, rigour of methods and statistical analyses, strength of trial

Results

Following revision to 2002, a subsequent review of Cochrane Library, PubMed and EBMR was carried out on publications to June 2004. Of the 113 articles retrieved, five RCTs were included in the chapter. The others were not relevant to Chapter 12 and were considered in Chapters 15, 16 and 19.

Comments

The original document was reviewed, the references checked and updated to current practice.

The references used in the articles were further examined for other related articles that may have been missed in the initial search. This review was extensive and thorough and carefully considered. Data that were flawed in a material way on the basis of methodology, exclusions, analysis, etc. were not used.

A large amount of the reference material was not directed at surgery in a 'pure' sense; it was also directed at chemotherapy and radiotherapy and so was not relevant in the context of this chapter as these data are covered in Chapters 16 and 19.

Chapter 13 — Emergency surgery

Search strategy

Cochrane databases, PubMed

Dates

Update of 1999 document from 1 January 1993 – 1 June 2004

Search terms

Colon cancer, rectal cancer, surgery, emergency

Inclusion/exclusion criteria

Excluded five foreign language papers and non-RCTs. There is no RCT of treatment versus no treatment.

Results

Search titles: PubMed — ten non-RCT citations, two RCTs (refs 22 and 15); the bona-fides of 15 RCTs are questioned in a Cochrane review by De Salvo et al (ref 16) that refers only to left-sided Colorectal Cancer.

Primary resection is standard practice for right colon obstruction; there are no RCTs.

Surgeons in Australia prefer primary resection for obstruction of both right colon and left colon. Current practice does not change on basis of no RCTs. There is no recommendation when there are no trials, merely advice to consider an approach based on observation. Cochrane review considers that this treatment 'has not yet been established as being more effective than a two stage procedure in patients with obstruction from primary left colon carcinoma'.¹ The lack of RCTs or favoured RCTs should not stop good things being done. Expert opinion is based on evidence level and strength of recommendation.

Comments

This chapter addresses clinical problems of patients with Colorectal Cancer who are in acute difficulty. The area addressed is quite deficient on randomised clinical trials. It is considered in Cochrane review that the variables involved in clinical circumstances render an RCT approach very difficult.

Cross-referencing to Chapter 10 is extensive

Chapter 14 — Clinicopathological staging and reporting

Search strategy

Cochrane Library, EBMR, Ovid, MD Consult, BMJ Clinical Evidence, PubMed.

Dates

Update of 1999 document. January 1998 – June 2004

Search terms

Clinicopathological staging, colon cancer, Colorectal Cancer, rectal cancer

Inclusion/exclusion criteria

Reference to the parameters of clinicopathological correlation with prognosis

Results

Two Cochrane systematic reviews and nine RCTs. One RCT not relevant. Hand searching, no further yield.

Clinicopathological staging, rectal cancer

PubMed — one RCT

Colorectal Cancer staging

Cochrane Library — three systematic reviews, nine RCTs

Clinical evidence — three

Ovid — 1 one review

MD Consult — three

PubMed — nine meta-analyses

PubMed — 85 RCTs

Comments

Clinicopathological staging and reporting involving use of minimum data set. The clinical and histological findings are outlined in Sections 14.1 and 14.2, including Tables 14.1, 14.2 and 14.3.

This chapter is essentially unchanged. It relates to ‘the classification of the tumour according to the extent of spread in a manner that has a clinically useful correlation with prognosis’.

References to specific imaging techniques such as MRI, PET and CT scanning do not relate to staging in its true sense; rather, they represent modalities of investigation for assessing the extent of the tumour spread at the time of diagnosis (see Chapter 8). Staging requires surgical and histopathological input as outlined in the guidelines to confer a stage on the tumour. Imaging modalities do not relate to prognosis in a statistically reproducible fashion and therefore, strictly speaking, they make no contribution to staging in the pure sense of the word.

There is no known, reliable preoperative staging system that correlates accurately with patient survival.

Chapter 15 and 16 — Adjuvant therapy for colon cancer and adjuvant therapy for rectal cancer

Search strategy

A systematic literature search was performed of the Medline database (January 1996 – January 2003). The Cochrane Library 2002 Issue 4 was also searched using the search phrases ‘colorectal’, ‘colon’, ‘rectal’ and ‘cancer’. A title alert was set up on Zetoc, the British Library Electronic Table of Contents service, using the terms ‘colon’ and ‘adjuvant’ (July 2002 – July 2003) to identify new articles as they were published. Hand searches were conducted of Conference Proceedings of the American Society of Clinical Oncology (1996–2003), the European Cancer Conference (1999, 2001, 2002), European Society of Therapeutic Radiation Oncology (2002) and the American Society for Therapeutic Radiation and Oncology (2001–2003).

Further searches of the Cochrane Database of Systematic Reviews, BMJ Clinical Evidence, Ovid, EBMR and PubMed to June 2004, using search terms ‘surgery’ and ‘rectal cancer’ revealed the following results.

Dates

Update of 1999 document from 1996 to 2004

Search terms

MeSH terms were ‘colorectal neoplasms’, ‘colonic neoplasms’, ‘rectal neoplasms’, ‘randomised controlled trials’ and ‘chemotherapy adjuvant’. Additional keywords used included ‘adjuvant’, ‘Colorectal Cancer’, publication type and ‘reviews’.

Inclusion/exclusion criteria

Relevance of reference. Quality of trials, and shortcomings where present, are discussed in text. All identified randomised trials not included in meta-analyses 4, 32, 44, 45 in Chapter 15 and 26, 27, 28 and 29 in Chapter 16 were included in references for the chapters.

Results

One hundred and thirteen (113) randomised trials were retrieved from PubMed 1 January 1998 to June 2004 and reviewed by the authors of Chapters 12, 15, 16 and 19. Most were not relevant to Chapters 15 and 16; however, seven trials were appropriate and incorporated into Chapters 15 and 16.

Comments

Recent review articles, meta-analyses and clinical guidelines were identified. The trials listed in these were crosschecked with references that were found by the searches above. The writing committee consisted of two authors who reviewed the trials. The chapters from the first edition of the guidelines were rewritten incorporating updates of trials and reviews in the original chapters, as well as the new trials identified. Formal meta-analysis was not carried out. The drafts were then circulated for external review by five medical oncologists, three radiation oncologists and three colorectal surgeons. Suggestions and feedback were incorporated in the drafts before they were considered by the main Working Party for these guidelines.

Chapter 17 — Follow up after curative resection for Colorectal Cancer

Search strategy

PubMed, Cochrane Library

Dates

Update of 1999 document from 1 January 1998 – 1 June 2004 (date limits extended if relevant article not previously cited)

Search terms

Follow up, curative resection, Colorectal Cancer

Inclusion/exclusion criteria

Headings of subsections in chapter served as search terms. Relevance to chapter subheadings if reference to be included.

Articles were excluded if they were not published in English; if they were not found to be relevant to the subject; if they were not relevant to Australian practices, for example, medication such as antibiotics not in routine use in Australia; or if the full publication was not readily available either online or through library resources.

Results

Two recent meta-analyses relating to intensive follow up and cost-effectiveness were identified and incorporated in the text. No other relevant studies were identified — most related to specific chemotherapeutic follow-up approaches.

Chapter 18 — Psychosocial care

Search strategy

Cochrane Library, PubMed

Dates

Update of 1999 document with search from 1 January 1998 to 1 June 2004

Search terms

Psychosocial care, cancer

Inclusion/exclusion criteria

Relevance to Colorectal Cancer

Results

A search of the Cochrane databases with the search terms 'psychosocial care' and 'cancer' yielded three systematic reviews that were not specific to Colorectal Cancer.

The register of controlled trials contained no trials relevant to Colorectal Cancer.

PubMed yielded 16 papers but their content was either not relevant to the chapter or was covered by the spectra of references.

Ovid, EBMR search and MD Consult Guidelines Research did not yield further information.

Comments

Clinical practice guidelines for the psychosocial care of adults with cancer (NBCC and NCCI 2003) was a significant source of tested reference material.

Chapter 19 — Recurrent and advanced Colorectal Cancer: general approach and local management (see Chapter 16)

Search strategy

As for Chapters 15 and 16

Dates

Updated 1999 document with search from January 1998 to June 2004

Search terms

Colon cancer, subsection headings

Results

This chapter was developed in consultation with the authors of Chapters 15 and 16.

Comments

The references from 1999 were reviewed and updated to June 2004.

Literature searches of PubMed and Cochrane reviews until June 2004 reveal scant good-quality clinical trials in which the treatment alternatives of surgery, medical oncology and radiation oncology have been compared. This situation often made the decision about the appropriate option both complex and difficult.

Chapter 20 — The role of systemic chemotherapy in metastatic disease and Chapter 21 — Management of liver and other distant metastases

Search strategy

Medline (1996–January 2003), The Cochrane Library 2002 Issue 4

A title alert was set up on Zetoc, the British Library Electronic Table of Contents service, using the terms ‘colon’ and ‘adjuvant’ (July 2002 – July 2003) to identify new articles as they were published. Hand searching of Conference Proceedings of the American Society of Clinical Oncology (1996–2003), the European Cancer Conference (1999, 2001, 2002), European Society of Therapeutic Radiation Oncology (2002) and the American Society for Therapeutic Radiation and Oncology (2001–2003).

Recent review articles, meta-analyses and clinical guidelines were identified and the trials listed in them were crosschecked with references were found by the searches listed above.

Dates

Update of 1999 document from 1996 to 2004

Search terms

As above, and including ‘radiotherapy’, ‘radiation oncology’, ‘peritoneal cytoreduction surgery’

PubMed: MeSH terms were ‘colorectal neoplasms’, ‘rectal neoplasms’, ‘randomised controlled trials’ and ‘chemotherapy metastatic’. Additional keywords used included ‘metastatic’, ‘Colorectal Cancer’, publication type and ‘reviews’.

Cochrane Library: ‘colorectal’, ‘colon’, ‘rectal’, ‘cancer’

Inclusion/exclusion criteria

Results

Extensions of review to 2004 with inclusion of Cochrane review comparing therapy as against no therapy. Inclusion of Cochrane review on adjuvant chemotherapy post liver resection. (Chapter 21). Peritoneal cytoreductive surgery was reviewed. PubMed 4 meta-analyses — all related to ovarian cancer and 45 RCTs, 2 relating to colorectal surgery. 3 Cochrane Systematic Reviews for cytoreductive surgery relate to glioma. This section was added to further address completeness in the current practice environment.

Comments

The writing committee consisted of two authors who reviewed the trials to ensure that the relevant studies that were used in treatment recommendations were randomised controlled trials. The chapters from the first edition of the Guidelines were rewritten incorporating updates of trials and reviews in the original chapters, as well as the new trials identified. Formal meta-analysis was not carried out. The drafts were then circulated for external review by two medical oncologists. Suggestions and feedback were incorporated in the drafts before consideration by the main Working Party for these Guidelines.

Chapter 22 —cost-effectiveness

Search strategy

A search was conducted using the databases Pre-Medline, Medline and Embase. Identified abstracts were scanned and all possible inclusions identified and obtained. The obtained articles were reviewed

and assessed based on the inclusion/exclusion criteria, and non-relevant articles were excluded. All remaining articles were thoroughly reviewed and summarised for inclusion in the guidelines.

Dates

January 1994 to December 2004

Search terms

Colorectal Cancer, colon cancer, rectal cancer, economic evaluation, cost-effectiveness analysis, cost benefit analysis, cost analysis and cost.

Inclusion/exclusion criteria

Articles were included if they were in English, judged to be economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences, or if they were reviews of economic evaluations.

Results

Possible inclusions originally identified: 164

Exclusions after review of articles: 43

Articles included in guidelines chapter: 121

Reasons for exclusion were as follows

1 = not English

29 = not relevant (not economic evaluation or predominately Colorectal Cancer)

4 = double (e.g. same study in different journals or original article and summary of same article)

9 = comprehensively reviewed in a systematic review already included

Comments

Of the 121 articles included in these guidelines, 49 investigated the effect of an intervention on outcomes such as lifeyears saved or gained or quality of life on utility, and seven were cost-benefit or cost-minimisation studies. A further 26 were cost and consequence analyses investigating the costs and effects of an intervention using limited measures of clinical outcome such as cancers detected, deaths prevented, cured or surviving patient, curative resection, recurrence/cured recurrence, and/or treating complications, or in some cases, output such as length of stay. The remainder consisted of 13 economic analyses that measured costs and outcomes/or outputs separately, four cost analyses measuring costs only, and 22 reviews or combined review/analyses.

The chapter also included four journals relating to the economic burden of cancer and the role of economic evidence in the development of guidelines of Colorectal Cancer.

Chapter 23 — Socioeconomic aspects in Colorectal Cancer

Search strategy

PubMed, Cochrane database

Dates

1990–2003

Search terms

Colorectal Cancer, socioeconomic, screening

Inclusion/exclusion criteria

RCT — relevance

Results

Eight RCTs — six used

Comments

Centred on compliance and avoided diet and medication implications

Assessment of evidence

General critical appraisal of literature followed the pattern listed below⁸ :

1. Were the treatments randomised?
2. Were there adequate controls?
3. Were sample sizes adequate?
4. Were exclusions specified and appropriate?
5. Were methods reproducible?
6. Were outcomes measured objectively?
7. Were results analysed statistically?
8. Was follow up complete?
9. Do results justify conclusions?

The guidelines are based on evidence that has been rated as level I, II, III-1, III-2, III-3 or IV according to the National Health and Medical Research Council (NHMRC) scale published in *A guide for the development, implementation and evaluation of clinical practice guidelines* (NHMRC 1999).²This scale does not include 'expert opinion', as did a former NHMRC scale used before publication of the 1999 guidelines. Accordingly, there are no formal guidelines based on expert opinion alone. Further research is required to provide evidence in these areas.

In accordance with the NHMRC handbook *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000), each recommendation has been further evaluated according to the level, quality and statistical precision of the included studies (strength of evidence), and the overall size and clinical importance of the effect. These detailed summations and other considerations, are included in each chapter.

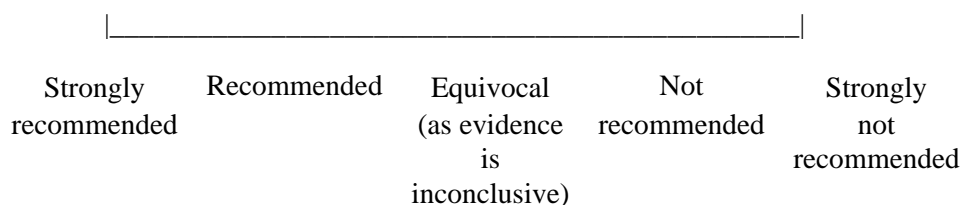
A clinical recommendation has been added alongside the level of evidence for each guideline to reproducibly interpret the expert panel's view of the overall strength of the recommendation. The background and clinical importance of each of the recommendations is fully discussed in the chapter that relates to them. The guidelines will be accompanied by a related document designed for the general practitioner and consumer.

Levels of evidence²

- I Evidence obtained from a systematic review of all relevant randomised controlled trials
- II Evidence obtained from at least one properly designed randomised controlled trial III-I Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method)
- III-2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
- III-3 Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
- IV Evidence obtained from case series, either post-test or pre-test/post-test

Strength of recommendations^{3,4}

The strength of recommendations is determined by the expert advisory panel and ranges from strongly recommended to strongly not recommended. These levels of recommendation are modified from The Canadian Task Force on the Periodic Health Examination.



To assign a level of recommendation, it was important for the clinical question to be clearly defined, for example:

‘Should prophylactic antibiotics be given for surgery for Colorectal Cancer’ (Section 10:6).

The evidence was then considered on a case-by-case basis taking into account the level of evidence, quality of studies, size of effect, and clinical importance for all the included studies. The following list shows examples of how the hierarchy of recommendations were applied:

- Strongly recommended** Clinically significant level I in favour of clinical question — strongly recommended in favour.
- Recommended** Clinically significant lower levels (e.g. II, III-1, III-2) in favour of clinical question — less strongly recommended in favour.
- Equivocal** Lack of higher levels of evidence (e.g. III-3 or IV) OR equivocal level I or II evidence for and against clinical question — no recommendation for or against, as evidence is inconclusive — recommend further research.
- Not recommended** Clinically significant lower levels (e.g. II, III-1, III-2) against the clinical question — weak recommendation against.
- Strongly not recommended** Clinically significant level I against the clinical question — strong recommendation against.

However, in some cases it was also necessary to take into account the best study types for particular clinical questions, such as cohort studies (level III-2) for questions of aetiology (risk) or prognosis. Therefore, for questions of aetiology and prognosis, a large body of good quality, clinically significant, level III-2 evidence was categorised “strongly recommended”. In other recommendations where there is a paucity of RCTs, the recommendation remains based on the accepted current practice, particularly where it is unlikely that there will be any RCTs conducted in the future.

References

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4. D. A. Grimes and Schulz K.A. An overview of clinical research, the lay of the land. *Lancet*, 359 (9300):57-61, 2002.