Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia

Copyright
The copyright owner of this publication is MaHTAS. Content may be reproduced in any number of copies and in any format or medium provided that a copyright acknowledgement to MaHTAS is included and the content is not changed, not sold, nor used to promote or endorse any product or service, and not used in an inappropriate or misleading context.


Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
http://maspho.org
http://haematology.org.my

Also available as an app for Android and IOS platform: MyMaHTAS

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.
UPDATING THE CPG

These guidelines were issued in 2018 and will be reviewed in a minimum period of four years (2022) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levels of Evidence and Formulation of Recommendation</td>
<td>i</td>
</tr>
<tr>
<td></td>
<td>Key Recommendations</td>
<td>ii</td>
</tr>
<tr>
<td></td>
<td>Guidelines Development and Objectives</td>
<td>iv</td>
</tr>
<tr>
<td></td>
<td>Development Group</td>
<td>vii</td>
</tr>
<tr>
<td></td>
<td>Review Committee</td>
<td>viii</td>
</tr>
<tr>
<td></td>
<td>External Reviewers</td>
<td>ix</td>
</tr>
<tr>
<td></td>
<td>Algorithm 1: Haemophilia Genetic Inheritance (X-linked)</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Algorithm 2: Genetic Testing for Haemophilia Patient and Carrier Screening</td>
<td>xi</td>
</tr>
<tr>
<td></td>
<td>Algorithm 3: Physiotherapy Management</td>
<td>xii</td>
</tr>
</tbody>
</table>

1. **INTRODUCTION**  

2. **CLINICAL PRESENTATION**  

3. **INVESTIGATIONS**  
   3.1 Laboratory Tests  
   3.2 Genetic Tests  

4. **GENERAL PRINCIPLES OF CARE**  
   4.1 Stratification of Haemophilia Centre with regards to Haemophilia Services  
   4.2 National Haemophilia Registry  

5. **TREATMENT**  
   5.1 Pharmacological Treatment  
     5.1.1 Factor Replacement Therapy  
     5.1.2 Adjunct Therapies  
     5.1.3 Analgesia  
   5.2 Non-pharmacological Treatment  
     5.2.1 Rehabilitation of Musculoskeletal System  
     5.2.2 Protection, Rest, Ice, Compression and Elevation  
     5.2.3 Joint Protection  
     5.2.4 Sports/physical Activity  
     5.2.5 Post-operative Care  
     5.2.6 Weight Management  

6. **TREATMENT FOR ACUTE BLEEDING IN SPECIFIC SITES**  
   6.1 Central Nervous System  
   6.2 Joints  
   6.3 Musculoskeletal  
   6.4 Ear, Nose, Throat and Eye  
   6.5 Gastrointestinal Tract
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6</td>
<td>Genitourinary Tract</td>
<td>27</td>
</tr>
<tr>
<td>6.7</td>
<td>Oral Cavity</td>
<td>28</td>
</tr>
</tbody>
</table>

7.   **TREATMENT OF MUSCULOSKELETAL COMPLICATIONS** 30

7.1 Synovitis 30
7.2 Joint Arthropathy 31
7.3 Pseudotumour 31

8.   **INHIBITORS** 33

8.1 Treatment of Acute Bleeding 34
8.2 Prophylaxis Therapy 34
8.3 Eradication of Inhibitors 35

9.   **HOME THERAPY** 37

10.  **ADHERENCE IN HAEMOPHILIA TREATMENT** 39

11.  **SPECIAL SITUATIONS** 41

11.1 Surgeries and Invasive Procedures 41
11.2 Management of Pregnant Carrier 42
11.3 Vaccination 43
11.4 Circumcision 43

12.  **DENTAL CARE** 44

12.1 Preventive Dental Measures 44
12.2 Dental Procedures 44
12.3 Management of Oral Bleeding 46

13.  **MONITORING** 48

13.1 Inhibitors 48
13.2 Bleeding Frequency 48
13.3 Joint Health 49
13.4 Radiological Measures 49

14.  **IMPLEMENTING THE GUIDELINES** 50

14.1 Facilitating and Limiting Factors 51
14.2 Potential Resource Implications 51

**REFERENCES** 53

Appendix 1 Example of Search Strategy 59
Appendix 2 Clinical Questions 60
Appendix 3 Guidelines on Sample Collection and Transportation 62
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appendix 4  Recommended Sports/Physical Activities in Haemophilia</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Appendix 5  Development of Abnormal Posture Following Bleeds</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Appendix 6  Face, Legs, Activity, Cry, Consolability (FLACC) Scale, Visual Analog Scale and Numeric Rating Scale</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Appendix 7  Analgesic Medication Table</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Appendix 8  Haemophilia Joint Health Score</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Appendix 9  Petterson Score</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>List of Abbreviations</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Acknowledgement</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Disclosure Statement</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Source of Funding</td>
<td>81</td>
</tr>
<tr>
<td>Level</td>
<td>Study design</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from at least one properly randomised controlled trial</td>
<td></td>
</tr>
<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trials without randomisation</td>
<td></td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group</td>
<td></td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees</td>
<td></td>
</tr>
</tbody>
</table>

**FORMULATION OF RECOMMENDATION**

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting *Grading Recommendations, Assessment, Development and Evaluation (GRADE)* in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

*SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001*
KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group (DG) as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Investigations

- Factor VIII or factor IX assay should be performed in persons suspected of haemophilia with prolonged Activated Partial Thromboplastin Time and normal Prothrombin Time.
- Mixing test should be done to screen for factor inhibitor in haemophilia.
  - If it is not corrected, Bethesda or Nijmegen assay should be done to determine the factor inhibitor level.
- Mutation analysis for haemophilia should be performed on affected male and his mother.
- Cascade screening for haemophilia should be offered to at least first- and second-degree female relatives if the mother of persons with haemophilia is a confirmed carrier.

Pharmacological Treatment

- Prophylactic factor infusion should be given to ALL persons with severe haemophilia.
- Analgesia should be offered for pain relief according to its severity in haemophilia.

Non-pharmacological Treatment

- Rehabilitation should be offered in PWH during acute or sub-acute bleeds and those with chronic arthropathy.
- Protection, Rest, Ice therapy, Compression, Elevation (PRICE) should be commenced as a first aid measure in acute and sub-acute bleed in persons with haemophilia.

Inhibitors

- Bypassing agents should be used to treat acute bleeding in haemophilia with inhibitors.
- Immune tolerance induction should be considered in all persons with haemophilia with inhibitor.
Home therapy

- Home therapy should be advocated to all persons with haemophilia.

Special Situations

- All injectable vaccinations in haemophilia should be given subcutaneously.

Dental Care

- In persons with haemophilia,
  - comprehensive oral health care should be initiated early within six months after the first tooth erupts and no later than 12 months
  - routine dental examination with preventive care measures should be conducted regularly throughout life
  - good oral hygiene and dietary counselling should be advocated to prevent dental diseases
- Comprehensive oral health care in haemophilia should be performed by a multidisciplinary team which include a dental surgeon.

Monitoring

- Monitoring of care in persons with haemophilia should include:
  - Annual Bleeding Rate
  - inhibitor screening
  - Annual Haemophilia Joint Health Score
  - ultrasound of knee, ankle and elbow when feasible
GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the DG for this CPG were from the Ministry of Health (MoH). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (refer to Appendix 1 for Example of Search Strategy). The search was limited to humans and English. In addition, the reference lists of all retrieved literature and guidelines were searched further to look for relevant studies. Experts in the field were also contacted to identify relevant studies. All searches were conducted from 6 March 2016 to 15 August 2018. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2018 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were made to other CPGs on haemophilia e.g.
- Guidelines for the Management of Haemophilia (World Federation of Haemophilia, 2012)
- Guidelines for the Management of Haemophilia in Australia (Australian Haemophilia Centre Directors’ Organisation, 2016)

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as references.

A total of 17 main clinical questions were developed under three different sections (screening, treatment and monitoring). Members of the DG were assigned individual questions within these sections (refer to Appendix 2 for Clinical Questions). The DG members met 26 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in their meetings. All statements and recommendations formulated subsequently were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001),
while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

Upon completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf).
OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of haemophilia in the following aspects:
   a) diagnosis
   b) treatment
   c) monitoring

CLINICAL QUESTIONS

Refer to Appendix 2.

TARGET POPULATION

Inclusion Criteria
   • All patients with congenital haemophilia A and B

Exclusion Criteria
   • Patients with:
     a. Acquired haemophilia
     b. Other congenital bleeding disorders

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of haemophilia including:
   i. doctors
   ii. allied health professionals
   iii. trainees and medical students
   iv. policy makers
   v. patients and their advocates
   vi. professional societies

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings
DEVELOPMENT GROUP

Chairperson

Dr. Zulaiha Muda
Consultant Paediatric Haemato-oncologist
Women & Children Hospital, Kuala Lumpur

Members (in alphabetical order)

Dr. Aisyah Muhammad Rivai
Consultant Paediatric Haemato-oncologist
Hospital Raja Permaisuri Bainun, Perak

Dr. Azman Othman
Family Medicine Specialist
Klinik Kesihatan Tengkera, Melaka

Dr. Cheah Yee Keat
Consultant Paediatrician
Hospital Tuanku Jaafar, Negeri Sembilan

Dr. Che Hadibiah Che Mohd Razali
Consultant Paediatric Haemato-oncologist
Hospital Sultan Ismail, Johor

Dato’ Dr. Goh Ai Sim
Senior Consultant Haematologist
Hospital Pulau Pinang, Pulau Pinang

Dr. Kamalia Kamarulzaman
Nuclear Medicine Physician
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Lim Soo Min
Consultant Haematologist
Hospital Sultanah Aminah, Johor

Dr. Mohd Aminuddin Mohd Yusof
Head of CPG Unit & Public Health Physician
MaHTAS, MoH, Putrajaya

Mr. Mohd Helmi Hashim
Physiotherapist
Hospital Ampang, Selangor

Dr. Nazzlin Dizana Din
Paediatric Haemato-oncologist
Hospital Sultanah Nur Zahirah, Terengganu

Dr. Nor’Ashikin Johari
Consultant Paediatric Orthopaedic Surgeon
Women & Children Hospital, Kuala Lumpur

Ms. Norhafizah Ayob
Physiotherapist
Women & Children Hospital, Kuala Lumpur

Dr. Norjehan Yahaya
Specialist in Special Needs Dentistry
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Ong Gek Bee
Consultant Paediatric Haemato-oncologist
Hospital Umum Sarawak, Sarawak

Dr. Raja Zarina Raja Shahardin
Consultant in Paediatric Dentistry
Women & Children Hospital, Kuala Lumpur

Ms. Siti Mariam Mohtar
Senior Assistant Director
MaHTAS, MoH, Putrajaya

Ms. Subasyini a/p Sivasupramaniam
Pharmacist
Women & Children Hospital, Kuala Lumpur

Dr. Wan Hayati Mohd Yaakob
Pathologist (Haematology)
Hospital Tuanku Ampuan Rahimah, Selangor
Management of Haemophilia

Ms. Wong Shu Ping  
Pharmacist  
Hospital Ampang, Selangor

Dr. Yeoh Seoh Leng  
Consultant Paediatric  
Haemato-oncologist  
Hospital Pulau Pinang, Pulau Pinang

Dr. Yuslina Mat Yusoff  
Pathologist (Haematology)  
Institut Penyelidikan Perubatan,  
Kuala Lumpur
REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of experts. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Dr. Hishamshah Mohd Ibrahim
Senior Consultant Paediatric Haematolo-oncologist
Head of Department
Paediatric Department
Women & Children Hospital, Kuala Lumpur

Members (in alphabetical order)

- Dr. Abd. Razak Muhamad, Consultant Paediatric Orthopaedic & Trauma Surgeon, Gleneagles Hospital, Kuala Lumpur
- Dr. Azlan Husin, Associate Professor, Consultant Physician & Clinical Haematologist, Hospital Universiti Sains Malaysia, Kelantan
- Dr. Carol Lim Kar Koong, Head of Department & Consultant Obstetrician & Gynaecologist (Maternal Fetal Medicine), Hospital Sultan Ahmad Shah, Pahang
- Ms. Haironi Ismail, Physiotherapist, Hospital Putrajaya, Putrajaya
- Ms. Halimah Hashim, Physiotherapist, Hospital Raja Perempuan Zainab II, Kelantan
- Dr. Jalil Ishak, Family Medicine Specialist, Klinik Kesihatan Jasin, Melaka
- Dr. Jameela Sathar, Senior Consultant Haematologist, Hospital Ampang, Selangor
- Dr. Junainah Sabirin, Deputy Director & Public Health Physician, MaHTAS, MoH, Putrajaya
- Dr. Lily Wong Lee Lee, Senior Consultant Haematologist, Hospital Queen Elizabeth, Sabah
- Prof. Dr. Noraini @ Nun Nahar Yunus, Professor in Paediatric Dentistry, Lincoln University College, Petaling Jaya, Selangor
- Ms. Norima Md. Noor, Pharmacist, Hospital Banting, Selangor
- Dr. Nik Rus Mazeni Nik Yusoff, Consultant Pathologist, Hospital Kuala Lumpur
- Mr. Taqrir Akramin Khalib, Patient Advocate & President, Pertubuhan Hemofilia Malaysia
- Dr. Zainah Shaikh Hedra, Consultant Paediatrician, Hospital Sultanah Nora Ismail, Johor
EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:

Dr. Ganasalingam Sockalingam  
Head of Department & Senior Consultant in Paediatric Dentistry  
Women & Children Hospital, Kuala Lumpur

Mr. Peit De Klient  
Physiotherapist  
UMC Utrecht Department of Rehabilitation  
Utrecht, Netherlands

Dr. Graeme Ting  
Consultant and Head of Discipline Special Needs Dentistry  
University of Otago, Dunedin, New Zealand

Dr. Ri Liesner  
Consultant in Paediatric Haemostasis and Thrombosis  
Great Ormond Street Hospital for Children  
London, United Kingdom

Dr. Jafanita Jamaluddin  
Senior Principal Assistant Director Obstetrics & Gynaecology, & Paediatrics Services Unit, Medical Development Division, MoH, Putrajaya

Dr. Ridzuan Dato’ Isa  
Head of Department & Emergency Physician  
Hospital Ampang, Selangor

Dr. Thiyagar Nadarajaw  
Head of Department & Consultant Paediatrician and Adolescent Medicine Specialist  
Hospital Sultanah Bahiyah, Kedah

Dr. Siti Zaleha Suleiman  
Family Medicine Specialist  
Klinik Kesihatan Merlimau, Melaka

Professor Mike Laffan  
Professor of Thrombosis and Haemostasis  
Imperial College London  
London, United Kingdom

Professor Dr. Wan Zaidah Abdullah  
Head of Department & Consultant Haematopathologist  
Hospital Universiti Sains Malaysia, Kelantan

Ms. Nor Hasni Haron  
Senior Principal Assistant Director Pharmaceutical Care Section Pharmacy Practice & Development Division  
MoH, Selangor
ALGORITHM 1. HAEMOPHILIA GENETIC INHERITANCE (X-LINKED)

A. Father with haemophilia Non-carrier mother (normal)

All sons are unaffected

50% chance of son will have haemophilia

50% chance of daughter will be carriers

B. Non-haemophilia father (normal) carrier mother

All daughters are carriers

50% chance of son will have haemophilia

50% chance of daughter will be carriers
ALGORITHM 2. GENETIC TESTING FOR HAEMOPHILIA PATIENT AND CARRIER SCREENING

Index case of haemophilia (diagnosed by factor assay)

Offer pre-test counselling to patient and parents and, obtain informed consent

Send specimen using ‘molecular analysis for haemophilia’ request form for each person*

Carrier status of mother is confirmed positive

Counselling

Counselling

Offer carrier screening for female siblings and maternal aunties

*Send samples in sodium citrate tubes of index case and both parents if testing is done in Pusat Darah Negara and in ethylenediaminetetraacetic acid tubes of index case and mother if testing is done in IMR. Refer to Appendix 3 on Guidelines on Sample Collection and Transportation.
**Management of Haemophilia**

**ALGORITHM 3. PHYSIOTHERAPY MANAGEMENT**

- **Active Bleeding**
  - **Acute (within 72 hours):**
    - PRICE
    - Protection (splint)
    - Rest
    - Ice
    - Compression
  - **Subacute (>3 days):**
    - Hydrotherapy
    - Mobilising exercise
    - Strengthening exercise
    - Mechanical exercise
  - **Chronic (>6 months):**
    - Hydrotherapy
    - Mobilising exercise
    - Strengthening exercise
    - Mechanical exercise
    - Weight-bearing exercise

- **Post-operative**
  - PRICE
  - Isometric exercise
  - Mobilisation
    - Active exercise
    - Bed mobility
    - Ambulation

- **Sports/physical activities**
  - All PWH should do regular sports/physical activities.
  - Refer to Appendix 4 for the type of sport/physical activities in relation to the risk of bleeding.

- All these activities are preferably carried out within 24-hour of factor infusion.
- Sports and physical fitness are important to maintain good muscle tone to protect the joints from the haemophilic-induced injuries, and these activities contribute to improvement in quality of life.
Pain severity is categorised in Table 8 and its management is described following it.

### Table 8. Category of pain

<table>
<thead>
<tr>
<th>Total pain score</th>
<th>Severity of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3</td>
<td>Mild</td>
</tr>
<tr>
<td>4 - 6</td>
<td>Moderate</td>
</tr>
<tr>
<td>7 - 10</td>
<td>Severe</td>
</tr>
</tbody>
</table>


Effectiveness of analgesics in PWH:
- Paracetamol is recommended for mild pain.\(^2\)
- Cyclooxygenase-2 (COX-2) inhibitors are effective analgesics:
  - celecoxib in chronic synovitis and non-specific mild to moderate pain\(^{25}\), level II-3
  - etoricoxib in haemophilic arthropathy\(^{26}\), level II-2
- Mild opioid is recommended as an alternative in moderate pain.\(^2\)
- If pain is moderate to severe in children, a strong opioid is necessary. Morphine is the opioid of choice.\(^{27}\), level III In haemophilia, morphine is recommended in severe pain.\(^2\)

Safety of analgesics in PWH:
- The risk of upper gastrointestinal bleeding increases by two-folds in traditional nonsteroidal anti-inflammatory drugs (NSAIDs) compared with celecoxib or rofecoxib in haemophilic arthropathy although it is statistically not significant.\(^{28}\), level II-2
- Celecoxib was noted to have no serious adverse events including hypertension or other CV events in a non-comparative study.\(^{25}\), level II-3
- Etoricoxib was noted to have higher bleeding duodenal ulcer, upper respiratory tract infection and headache compared with placebo (\(p=0.043\)) in a cohort study.\(^{26}\), level II-2