

# How to get your paper published in an English language Journal

---

Dr. Gordon S. Doig  
Associate Professor in Intensive Care  
Northern Clinical School Intensive Care Research Unit,  
University of Sydney, Sydney, Australia  
[www.EvidenceBased.net](http://www.EvidenceBased.net)  
[gdoig@med.usyd.edu.au](mailto:gdoig@med.usyd.edu.au)

© 2017, University of Sydney, Not for reproduction or distribution.





# Editorial responsibilities

- Section Editor at ICM

The screenshot shows the top part of the ICM website. The logo 'icm' is in a large, blue, lowercase font. Below it, 'INTENSIVE CARE MEDICINE' is written in a smaller, blue, uppercase font. Underneath that, a dark blue banner contains the text 'OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE AND THE EUROPEAN SOCIETY OF PAEDIATRIC & NEONATAL INTENSIVE CARE' in white, uppercase letters. Below the banner is a search bar with a dropdown menu set to 'All issues', the word 'for', and a 'SEARCH' button. Below the search bar is a group photo of the ICM Editorial Board members from 2016, standing on a staircase in a grand, well-lit room with large windows and framed pictures on the wall.

**ICM Editorial Board 2016**



# Editorial responsibilities

- Section Editor at ICM

**icm**  
INTENSIVE CARE MEDICINE

OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE  
AND THE EUROPEAN SOCIETY OF PAEDIATRIC & NEONATAL INTENSIVE CARE

All issues ▾ for  SEARCH

ICM Editorial Board 2016



# Editorial responsibilities

- Section Editor at ICM

- Editorial Board Member for CCM



ICM Editorial Board 2016

Editorial Board

## Critical Care Medicine

<p><b>EDITORIAL BOARD MEMBERS</b></p> <p><b>Edward Abraham, MD, FCCM</b> Professor and Dean Wake Forest School of Medicine Winston-Salem, North Carolina</p> <p><b>Hasan B. Alam, MD, FACS</b> Professor of Surgery Harvard Medical School Program Director, Surgical Critical Care Fellowship Program Massachusetts General Hospital Boston, Massachusetts</p> <p><b>Theodore A. Alston, MD, PhD</b> Department of Anesthesia, Critical Care, and Pain Medicine Massachusetts General Hospital Harvard Medical School Boston, Massachusetts</p> <p><b>John H. Arnold, MD</b> Professor of Anaesthesia (Pediatrics) Harvard Medical School Senior Associate, Anesthesia and Critical Care Medical Director, Respiratory Care/ECMO Boston Children's Hospital Boston, Massachusetts</p> <p><b>Philip S. Barie, MD, MBA, MCCM</b> Professor of Surgery and Public Health Weill Cornell Medical College New York, New York</p> <p><b>Anish Bhardwaj, MD, MBA, CPE, FAHA, FCCM, FAAN, FANA</b></p>	<p><b>Charles Cairns, MD</b> Dean, College of Medicine Professor, Department of Emergency Medicine Assistant Vice President, Clinical Research University of Arizona Health Sciences Tucson, Arizona</p> <p><b>Cherylee W. Chang, MD, FCCM</b> Associate Clinical Professor Department of Medicine and Surgery The Queen's Medical Center, University of Hawaii, John Burns School of Medicine Honolulu, Hawaii</p> <p><b>Daive Chiumello, MD</b> Dipartimento di Anestesia, Rianimazione Emergenza Urgenza Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milan, Italy</p> <p><b>David A. Cook, PhD, FANZCA, FCICM</b> Professor of Anaesthesia and Critical Care Intensive Care Unit Princess Alexandra Hospital Brisbane, Australia</p> <p><b>Craig M. Coopersmith, MD, FCCM</b> Professor of Surgery Emory Center for Critical Care Emory University School of Medicine Atlanta, Georgia</p> <p><b>Douglas B. Coursin, MD</b> Professor, Anesthesiology and Medicine University of Wisconsin School of Medicine and Public Health Madison, Wisconsin</p> <p><b>Elliott Crouser, MD</b> Associate Professor of Medicine</p>	<p><b>John W. Devlin, PharmD, FCCP, FCCM</b> Professor, Department of Pharmacy Practice Bouve College Northeastern University Special and Scientific Staff Division of Pulmonary, Critical Care and Sleep Medicine Tufts Medical Center Boston, Massachusetts</p> <p><b>Gordon S. Doig, PhD</b> Head, Northern Clinical School Intensive Care Research Unit University of Sydney Royal North Shore Hospital Sydney, Australia</p> <p><b>Todd Dorman, MD</b> Senior Associate Dean for Education Coordination Associate Dean for CME Professor and Vice Chair for Critical Care Department of Anesthesiology and Critical Care Medicine Joint Appointments in Internal Medicine, Surgery, and the School of Nursing Johns Hopkins University School of Medicine Baltimore, Maryland</p> <p><b>David J. Dries, MSE, MD, MCCM</b> Assistant Medical Director for Surgical Care Health Partners Medical Group, Regions Hospital Professor of Surgery and Anesthesiology University of Minnesota Saint Paul, Minnesota</p> <p><b>Philip A. Efron, MD, FACS, FCCM</b> Associate Professor, Departments of Surgery</p>
--	---	---



# Editorial responsibilities

- Section Editor at ICM

- Editorial Board Member for CCM



ICM Editorial Board 2016

Editorial Board

## Critical Care Medicine

**EDITORIAL BOARD MEMBERS**

**Edward Abraham, MD, FCCM**  
Professor and Dean  
Wake Forest School of Medicine  
Winston-Salem, North Carolina

**Hasan B. Alam, MD, FACS**  
Professor of Surgery  
Harvard Medical School  
Program Director, Surgical Critical Care Fellowship Program  
Massachusetts General Hospital  
Boston, Massachusetts

**Theodore A. Alston, MD, PhD**  
Department of Anesthesia, Critical Care, and Pain Medicine  
Massachusetts General Hospital  
Harvard Medical School  
Boston, Massachusetts

**John H. Arnold, MD**  
Professor of Anaesthesia (Pediatrics)  
Harvard Medical School  
Senior Associate, Anesthesia and Critical Care  
Medical Director, Respiratory Care/ECMO  
Boston Children's Hospital  
Boston, Massachusetts

**Philip S. Barie, MD, MBA, MCCM**  
Professor of Surgery and Public Health  
Weill Cornell Medical College  
New York, New York

**Anish Bhardwaj, MD, MBA, CPE, FAHA, FCCM, FAAN, FANA**

**Charles Cairns, MD**  
Dean, College of Medicine  
Professor, Department of Emergency Medicine  
Assistant Vice President, Clinical Research  
University of Arizona Health Sciences  
Tucson, Arizona

**Cherylee W. Chang, MD, FCCM**  
Associate Clinical Professor  
Department of Medicine and Surgery  
The Queen's Medical Center, University of Hawaii, John Burns School of Medicine  
Honolulu, Hawaii

**Daive Chiumello, MD**  
Dipartimento di Anestesia, Rianimazione  
Emergenza Urgenza  
Fondazione IRCCS Ca' Granda  
Ospedale Maggiore Policlinico  
Milan, Italy

**David A. Cook, PhD, FANZCA, FCICM**  
Professor of Anaesthesia and Critical Care  
Intensive Care Unit  
Princess Alexandra Hospital  
Brisbane, Australia

**Craig M. Coopersmith, MD, FCCM**  
Professor of Surgery  
Emory Center for Critical Care  
Emory University School of Medicine  
Atlanta, Georgia

**Douglas B. Coursin, MD**  
Professor, Anesthesiology and Medicine  
University of Wisconsin School of Medicine and Public Health  
Madison, Wisconsin

**Elliott Crouser, MD**  
Associate Professor of Medicine

**John W. Devlin, PharmD, FCCP, FCCM**  
Professor, Department of Pharmacy Practice  
Bouve College  
Northeastern University  
Special and Scientific Staff  
Division of Pulmonary, Critical Care and Sleep Medicine  
Critical Care Pharmacist  
Tufts Medical Center  
Boston, Massachusetts

**Gordon S. Doig, PhD**  
Head, Northern Clinical School  
Intensive Care Research Unit  
University of Sydney  
Royal North Shore Hospital  
Sydney, Australia

**Todd Dorman, MD**  
Senior Associate Dean for Education  
Coordination  
Associate Dean for CME  
Professor and Vice Chair for Critical Care  
Department of Anesthesiology and Critical Care Medicine  
Joint Appointments in Internal Medicine, Surgery, and the School of Nursing  
Johns Hopkins University School of Medicine  
Baltimore, Maryland

**David J. Dries, MSE, MD, MCCM**  
Assistant Medical Director for Surgical Care  
Health Partners Medical Group,  
Regions Hospital  
Professor of Surgery and Anesthesiology  
University of Minnesota  
Saint Paul, Minnesota

**Philip A. Efron, MD, FACS, FCCM**  
Associate Professor, Departments of Surgery



## Reviewer

---

2014-present, American Journal of Clinical Nutrition  
 2014-present, Intensive Care Medicine Experimental  
 2014-present, Lipids in Health and Disease  
 2014-present, Advances in Medical Education and Practice  
 2013-present, Journal of Pain and Symptom Management  
 2013-present, Saudi Medical Journal  
 2013-present, Patient Preference and Adherence  
 2012-present, Journal of Clinical Epidemiology  
 2012-present, American Journal of Respiratory and Critical Care Medicine  
 2011-present, New England Journal of Medicine  
 2010-present, Acta Anaesthesiologica Scandinavica  
 2009-present, Canadian Medical Association Journal  
 2009-present, Journal of Parenteral and Enteral Nutrition

2009-present, Critical Care and Resuscitation  
 2009-present, Injury  
 2009-present, Clinical Nutrition  
 2009-present, Respirology  
 2008-present, British Medical Journal  
 2008-present, Journal of the American Medical Association  
 2008-present, British Journal of Nutrition  
 2008-present, Asia Pacific Journal of Clinical Nutrition  
 2008-present, Hemodialysis International,  
 2008-present, Anesthesia & Analgesia  
 2006-present, Journal of Critical Care  
 2005-present, Critical Care  
 2004-present, Anaesthesia and Intensive Care  
 2003-present, Intensive Care Medicine  
 2002-present, Critical Care Medicine  
 1999-present, Chest



## Reviewer

2014-present, American Journal of Clinical Nutrition  
 2014-present, Intensive Care Medicine Experimental  
 2014-present, Lipids in Health and Disease  
 2014-present, Advances in Medical Education and Practice  
 2013-present, Journal of Pain and Symptom Management  
 2013-present, Saudi Medical Journal  
 2013-present, Patient Preference and Adherence  
 2012-present, Journal of Clinical Epidemiology  
 2012-present, American Journal of Respiratory and Critical Care Medicine  
 2011-present, **New England Journal of Medicine**  
 2010-present, Acta Anaesthesiologica Scandinavica  
 2009-present, Canadian Medical Association Journal  
 2009-present, Journal of Parenteral and Enteral Nutrition

2009-present, Critical Care and Resuscitation  
 2009-present, Injury  
 2009-present, Clinical Nutrition  
 2009-present, Respirology  
 2008-present, **British Medical Journal**  
 2008-present, **Journal of the American Medical Association**  
 2008-present, British Journal of Nutrition  
 2008-present, Asia Pacific Journal of Clinical Nutrition  
 2008-present, Hemodialysis International,  
 2008-present, Anesthesia & Analgesia  
 2006-present, Journal of Critical Care  
 2005-present, Critical Care  
 2004-present, Anaesthesia and Intensive Care  
 2003-present, Intensive Care Medicine  
 2002-present, Critical Care Medicine  
 1999-present, Chest



**icm** | THE OFFICIAL JOURNAL OF |

**ESICM** | Society of Intensive Care Medicine

**INTENSIVE CARE MEDICINE**





---

1,038 original research papers (observational study, RCT) were received in 2015



1,038 original research papers (observational study, RCT) were received in 2015

- **63%** (654/1,038) rejected by Editor
  - Never sent to external reviewers
  - Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.



1,038 original research papers (observational study, RCT) were received in 2015

- 63% (654/1,038) rejected by Editor
  - Never sent to external reviewers
  - Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.

348 of 1,038 papers sent by Editor to external reviewers



1,038 original research papers (observational study, RCT) were received in 2015

- **63%** (654/1,038) rejected by Editor
  - Never sent to external reviewers
  - Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.

348 of 1,038 papers sent by Editor to external reviewers

- **86%** (301/348) rejected after negative comments from reviewers
  - Reviewers determine bad study, poorly explained or poorly written.
  - *Sometimes* reviewers determine content not appropriate for journal or content not interesting to journal.
  - *Sometimes* reviewers recommend Reject after Authors fail to make recommended corrections!



1,038 original research papers (observational study, RCT) were received in 2015

- **63%** (654/1,038) rejected by Editor
  - Never sent to external reviewers
  - Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.

348 of 1,038 papers sent by Editor to external reviewers

- **86%** (301/348) rejected after negative comments from reviewers
  - Reviewers determine bad study, poorly explained or poorly written.
  - *Sometimes* reviewers determine content not appropriate for journal or content not interesting to journal.
  - *Sometimes* reviewers recommend Reject after Authors fail to make recommended corrections!

83 submissions accepted

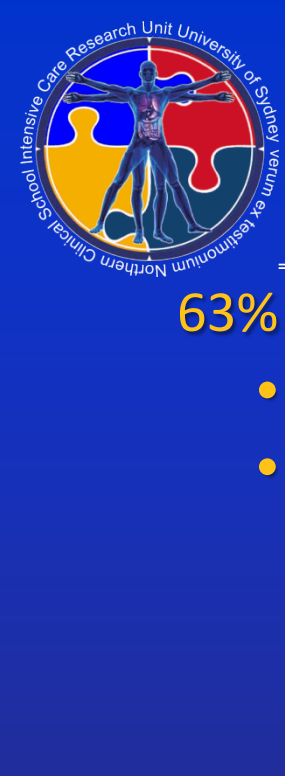
- **8%** (83/1,038) of total submissions!!!



## *Summary of this talk*

---

- Perspective of an Editor, Reviewer and Researcher.
- Avoiding rejection by the Editor
- Avoiding rejection by Reviewers
- Responding to Reviewers Comments
- General Insights
- Summary



## *Avoiding rejection by Editor*

---

**63%** (654/1,038) rejected by Editor

- Never sent to external reviewers
- Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.



## *Avoiding rejection by Editor*

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.*





## Avoiding rejection by Editor

---

Editor determines *content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.*

Undertake journal selection *before* you start your research project.

- Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.
- Use these papers as a guide for journal selection *and* study design.



## Avoiding rejection by Editor

Editor determines *content not appropriate for journal, content not interesting to journal, very bad study, very poorly written.*

Undertake journal selection *before* you start your research project.

- Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.
- Use these papers as a guide for journal selection *and* study design.

If you cannot find a project like your intended study published in your target journal, choose another journal.

- **Ex.** ICM does not publish animal laboratory work or single centre retrospective observational data.



## *Avoiding rejection by Editor*

---

*Editor determines content not appropriate for journal, content not interesting to journal, **very bad study**, very poorly written.*



## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, **very bad study**, very poorly written.*

Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.

- Read these papers thoroughly:
  - They have successfully made it through the review process!
  - They can teach us journal preferences, good study design and good presentation styles.



## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, **very bad study**, very poorly written.*

Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.

- Read these papers thoroughly:
  - They have successfully made it through the review process!
  - They can teach us journal preferences, good study design and good presentation styles.

Ensure your study collects and presents information in a similar way to other papers published in your target journals.

- Severity of illness for ICU patients is traditionally captured with APACHE score in the US but SAPS score in Europe.



## *Avoiding rejection by Editor*

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*



## *Avoiding rejection by Editor*

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.



## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.





## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.
- The *easiest* decision for a Editor to make is '**Reject without Review**'.
  - Immediately removes work from their inbox.
  - Reduces future work, as they will never see the paper again!



## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.
- The *easiest* decision for a Editor to make is '**Reject without Review**'.
  - Immediately removes work from their inbox.
  - Reduces future work, as they will never see the paper again!

Because Editors are busy, there is only **one** section of your paper you can guarantee an Editor will read:



## Avoiding rejection by Editor

---

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.
- The *easiest* decision for a Editor to make is '**Reject without Review**'.
  - Immediately removes work from their inbox.
  - Reduces future work, as they will never see the paper again!

Because Editors are busy, there is only **one** section of your paper you can guarantee an Editor will read:

- It is usually the section we write last, when we are tired.
- We put the least effort into it, yet it might be the most important section.



## Avoiding rejection by Editor

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.
- The *easiest* decision for a Editor to make is '**Reject without Review**'.
  - Immediately removes work from their inbox.
  - Reduces future work, as they will never see the paper again!

Because Editors are busy, there is only **one** section of your paper you can guarantee an Editor will read:

- It is usually the section we write last, when we are tired.
- We put the least effort into it, yet it might be the most important section.

If your **Abstract** is poorly written, you make it easy for the Editor to '**Reject without Review**'!



# *Lancet, Respiratory Medicine*

---



# Lancet, Respiratory Medicine

## Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial

John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darinr Sosohtikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

**Findings** Beginning in March 15, 2012, 92 patients were enrolled, and the trial was completed on Jan 2, 2014. 63 patients were assigned to receive eltrombopag and 29 were assigned to receive placebo. In the double-blind period, three patients discontinued treatment because of adverse events: two patients in the eltrombopag group withdrew because of increased liver aminotransferases and one in the placebo group withdrew because of abdominal haemorrhage. 25 (40%) patients who received eltrombopag compared with one (3%) patient who received placebo achieved the primary outcome of platelet counts of at least  $50 \times 10^9$  per L for 6 of the last 8 weeks of the double-blind period (odds ratio 18.0, 95% CI, 2.3–140.9;  $p=0.0004$ ). Responses were similar in all cohorts (eltrombopag vs placebo: 39% vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years). Proportionately fewer patients who received eltrombopag (23 [37%] of 63 patients) had WHO grades 1–4 bleeding at the end of the double-blind period than did those who received placebo (16 [55%] of 29 patients); grades 2–4 bleeding were similar (three [5%] patients who received eltrombopag vs two [7%] patients who received placebo). During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.



Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)00114-3](http://dx.doi.org/10.1016/S0140-6736(15)00114-3)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)01223-5](http://dx.doi.org/10.1016/S0140-6736(15)01223-5)

See Online/Articles Lancet Haem 2015; published online July 29.  
[http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (E Donyush MD); Siriraj Hospital, Bangkok, Thailand (B Pongtanakul MD); Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand (P Komvilaisak MD); Chulalongkorn University, Bangkok, Thailand (D Sosohtikul MD); Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina (G Drelichman MD); Ramathibodi Hospital, Bangkok, Thailand (N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (C Bailey MD).



# Lancet, Respiratory Medicine

## Journal Style Sheet

### Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial

John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darinr Sosohtikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

#### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

**Findings** Beginning in March 15, 2012, 92 patients were enrolled, and the trial was completed on Jan 2, 2014. 63 patients were assigned to receive eltrombopag and 29 were assigned to receive placebo. In the double-blind period, three patients discontinued treatment because of adverse events: two patients in the eltrombopag group withdrew because of increased liver aminotransferases and one in the placebo group withdrew because of abdominal haemorrhage. 25 (40%) patients who received eltrombopag compared with one (3%) patient who received placebo achieved the primary outcome of platelet counts of at least  $50 \times 10^9$  per L for 6 of the last 8 weeks of the double-blind period (odds ratio 18.0, 95% CI, 2.3–140.9;  $p=0.0004$ ). Responses were similar in all cohorts (eltrombopag vs placebo: 39% vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years). Proportionately fewer patients who received eltrombopag (23 [37%] of 63 patients) had WHO grades 1–4 bleeding at the end of the double-blind period than did those who received placebo (16 [55%] of 29 patients); grades 2–4 bleeding were similar (three [5%] patients who received eltrombopag vs two [7%] patients who received placebo). During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.



Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)00114-3](http://dx.doi.org/10.1016/S0140-6736(15)00114-3)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)01223-5](http://dx.doi.org/10.1016/S0140-6736(15)01223-5)

See Online/Articles Lancet Haem  
 2015; published online July 29.  
[http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (E Donyush MD); Siriraj Hospital, Bangkok, Thailand (B Pongtanakul MD); Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand (P Komvilaisak MD); Chulalongkorn University, Bangkok, Thailand (D Sosohtikul MD); Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina (G Drelichman MD); Ramathibodi Hospital, Bangkok, Thailand (N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (C K Bailey MD).



# Lancet, Respiratory Medicine

## Journal Style Sheet

## Background:

## Introduction

## Findings:

## Results:

## Interpretation:

## Conclusions:

### Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial

John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darinr Sosohtikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

#### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

**Findings** Beginning in March 15, 2012, 92 patients were enrolled, and the trial was completed on Jan 2, 2014. 63 patients were assigned to receive eltrombopag and 29 were assigned to receive placebo. In the double-blind period, three patients discontinued treatment because of adverse events: two patients in the eltrombopag group withdrew because of increased liver aminotransferases and one in the placebo group withdrew because of abdominal haemorrhage. 25 (40%) patients who received eltrombopag compared with one (3%) patient who received placebo achieved the primary outcome of platelet counts of at least  $50 \times 10^9$  per L for 6 of the last 8 weeks of the double-blind period (odds ratio 18.0, 95% CI, 2.3–140.9;  $p=0.0004$ ). Responses were similar in all cohorts (eltrombopag vs placebo: 39% vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years). Proportionately fewer patients who received eltrombopag (23 [37%] of 63 patients) had WHO grades 1–4 bleeding at the end of the double-blind period than did those who received placebo (16 [55%] of 29 patients); grades 2–4 bleeding were similar (three [5%] patients who received eltrombopag vs two [7%] patients who received placebo). During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.



Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)00114-3](http://dx.doi.org/10.1016/S0140-6736(15)00114-3)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)01223-5](http://dx.doi.org/10.1016/S0140-6736(15)01223-5)

See Online/Articles Lancet Haem  
 2015; published online July 29.  
[http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (E Donyush MD); Siriraj Hospital, Bangkok, Thailand (B Pongtanakul MD); Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand (P Komvilaisak MD); Chulalongkorn University, Bangkok, Thailand (D Sosohtikul MD); Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina (G Drelichman MD); Ramathibodi Hospital, Bangkok, Thailand (N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (C Bailey MD).





# Lancet, Respiratory Medicine

## Journal Style Sheet

## Background:

## Introduction

## Findings:

## Results:

## Interpretation:

## Conclusions:

### Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial

John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darinri Sosothikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

#### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

**Findings** Beginning in March 15, 2012, 92 patients were enrolled, and the trial was completed on Jan 2, 2014. 63 patients were assigned to receive eltrombopag and 29 were assigned to receive placebo. In the double-blind period, three patients discontinued treatment because of adverse events: two patients in the eltrombopag group withdrew because of increased liver aminotransferases and one in the placebo group withdrew because of abdominal haemorrhage. 25 (40%) patients who received eltrombopag compared with one (3%) patient who received placebo achieved the primary outcome of platelet counts of at least  $50 \times 10^9$  per L for 6 of the last 8 weeks of the double-blind period (odds ratio 18.0, 95% CI, 2.3–140.9;  $p=0.0004$ ). Responses were similar in all cohorts (eltrombopag vs placebo: 39% vs 10% for patients aged 12–17 years, 42% vs 0% for patients aged 6–11 years, and 36% vs 0% for patients aged 1–5 years). Proportionately fewer patients who received eltrombopag (23 [37%] of 63 patients) had WHO grades 1–4 bleeding at the end of the double-blind period than did those who received placebo (16 [55%] of 29 patients); grades 2–4 bleeding were similar (three [5%] patients who received eltrombopag vs two [7%] patients who received placebo). During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.



Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)00114-3](http://dx.doi.org/10.1016/S0140-6736(15)00114-3)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)01223-5](http://dx.doi.org/10.1016/S0140-6736(15)01223-5)

See Online/Articles Lancet Haem  
 2015; published online July 29.  
[http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (E Donyush MD); Siriraj Hospital, Bangkok, Thailand (B Pongtanakul MD); Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand (P Komvilaisak MD); Chulalongkorn University, Bangkok, Thailand (D Sosothikul MD); Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina (G Drelichman MD); Ramathibodi Hospital, Bangkok, Thailand (N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (U Ramenghi MD).



# Lancet, Respiratory Medicine

## Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial



John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darintr Sosothikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)00114-3](http://dx.doi.org/10.1016/S0140-6736(15)00114-3)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)01223-5](http://dx.doi.org/10.1016/S0140-6736(15)01223-5)

See Online/Articles Lancet Haem 2015; published online July 29.  
[http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (V Lebedev MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (U Ramenghi MD).

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.

During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.

(N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (U Ramenghi MD).



# Lancet, Respiratory Medicine

## Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial



John D Grainger, Franco Locatelli, Thirachit Chotsampancharoen, Elena Donyush, Bunchoo Pongtanakul, Patcharee Komvilaisak, Darintr Sosothikul, Guillermo Drelichman, Nongnuch Srachainan, Susanne Holzhauer, Vladimir Lebedev, Richard Lemons, Dagmar Pospisilova, Ugo Ramenghi, James B Bussel, Kalpana K Bakshi, Malini Iyengar, Geoffrey W Chan, Karen D Chagin, Dickens Theodore, Lisa M Marcella, Christine K Bailey

### Summary

**Background** The thrombopoietin receptor agonist eltrombopag has been shown to be safe, tolerable, and effective for adults with chronic immune thrombocytopenia. We aimed to investigate the safety and efficacy of eltrombopag for children with chronic immune thrombocytopenia.

**Methods** PETIT2 was a two part, randomised, multicentre, placebo-controlled study done at 38 centres in 12 countries (Argentina, Czech Republic, Germany, Hong Kong, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA). Paediatric patients aged 1–17 years who had chronic immune thrombocytopenia and platelet counts less than  $30 \times 10^9$  per L were randomly assigned (2:1) to receive eltrombopag or placebo. We stratified patients by age into three cohorts (patients aged 12–17 years, 6–11 years, and 1–5 years) before randomly entering them into a 13 week, double-blind period. Randomisation was done by the GlaxoSmithKline Registration and Medication Ordering System and both patients and study personnel were masked to treatment assignments. Patients who were allocated eltrombopag received tablets (except for those aged 1–5 years who received an oral suspension formulation) once per day for 13 weeks. Starting doses for patients aged 6–17 were based on bodyweight, and ethnic origin and ranged between 50 mg/day and 25 mg/day (starting dose for patients aged 1–5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for east Asian patients). Patients who completed the double-blind period entered a 24 week open-label treatment period in which all patients received eltrombopag at either the starting dose (if they were formerly on placebo) or their established dose. The primary outcome was the proportion of patients achieving platelet counts of at least  $50 \times 10^9$  per L in the absence of rescue therapy for 6 or more weeks from weeks 5 to 12 of the double-blind period. The intention-to-treat population included in the efficacy assessment consisted of all patients who were randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

Published Online

July 29, 2015  
[http://dx.doi.org/10.1016/S0140-6736\(15\)61107-2](http://dx.doi.org/10.1016/S0140-6736(15)61107-2)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(15\)61223-5](http://dx.doi.org/10.1016/S0140-6736(15)61223-5)

See Online/Articles Lancet Haem 2015; published online July 29, 2015; [http://dx.doi.org/10.1016/S2352-3026\(15\)00114-3](http://dx.doi.org/10.1016/S2352-3026(15)00114-3)

Department of Haematology, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK (J D Grainger MD); IRCCS Ospedale Pediatrico Bambino Gesù, University of Pavia, Rome, Italy (F Locatelli MD); Prince of Songkla University, Songklanagarind Hospital, Bangkok, Thailand (T Chotsampancharoen MD); Izmaylovskaya Children's City Clinical Hospital, Moscow Board of Health, Moscow, Russia (V Lebedev MD); Faculty of Medicine, University of Cologne, Cologne, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (U Ramenghi MD)

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.

During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.

(N Srachainan MD); Charité University Medicine, Berlin, Germany (S Holzhauer MD); GIZ Regional Children's Clinical Hospital, Krasnodar, Russia (V Lebedev MD); Primary Children's Medical Center, Salt Lake City, UT, USA (R Lemons MD); Faculty Hospital of Palacky University, Olomouc, Czech Republic (D Pospisilova MD); Regina Margherita Children's Hospital, Turin, Italy (U Ramenghi MD)



## Lancet, Respiratory Medicine

Eltrombopag for children with chronic immune



**Conclusions** In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. (N Engl J Med 2000;342:1301-8.)

©2000, Massachusetts Medical Society.

randomly assigned to one of the treatment groups, and the safety population included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01520909.

Izmaylovskaya Children's City  
Clinical Hospital, Moscow  
Board of Health, Moscow.

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.

During the 24-week open-label treatment period, 70 [80%] of 87 patients achieved platelet counts of  $50 \times 10^9$  per L or more at least once. Adverse events that occurred more frequently with eltrombopag than with placebo included nasopharyngitis (11 [17%] patients), rhinitis (10 [16%] patients), upper respiratory tract infection (7 [11%] patients), and cough (7 [11%] patients). Serious adverse events occurred in five (8%) patients who received eltrombopag and four (14%) who received placebo. Safety was consistent between the open-label and double-blind periods. No deaths, malignancies, or thromboses occurred during the trial.

(N Sirachainan MD); Charité,  
University Medicine, Berlin,  
Germany (S Hohsauer MD);  
GIZ Regional Children's Clinical  
Hospital, Krasnodar, Russia  
(V Lebedev MD); Primary  
Children's Medical Center, Salt  
Lake City, UT, USA  
(R Lemons MD); Faculty  
Hospital of Palacky University,  
Olomouc, Czech Republic  
(D Pospisilova MD); Regina  
Margherita Children's Hospital,  
Turin, Italy (M Pavesio MD).

**Interpretation** Eltrombopag, which produced a sustained platelet response in 40% of patients with chronic immune thrombocytopenia, is a suitable therapeutic option for children with chronic symptomatic immune thrombocytopenia. We identified no new safety concerns and few patients discontinued treatment because of adverse events.



# Lancet, Respiratory Medicine

## Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial



Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter W J Harrigan, for the Refeeding Syndrome Trial Investigators Group\*

### Summary

**Background** Equipose exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

**Methods** We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration ( $>0.32$  mmol/L vs  $\leq 0.32$  mmol/L) and body-mass index (BMI;  $>18$  kg/m<sup>2</sup> vs  $\leq 18$  kg/m<sup>2</sup>). The primary outcome was the number of days alive after ICU discharge, with 60 day follow-up, in a modified intention-to-treat population of all randomly allocated patients except those mistakenly enrolled. Days alive after ICU discharge was a composite outcome based on ICU length of stay, overall survival time, and mortality. The Refeeding Syndrome Trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR number 12609001043224).

**Findings** Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39.9 (95% CI 36.4–43.7) compared with 44.8 (95% CI 40.9–49.1) in 166 assessable patients in the caloric restriction group (difference 4.9 days, 95% CI –2.3 to 13.6,  $p=0.19$ ). Nevertheless, protocolised caloric restriction improved key individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 vs 149 [91%] of 164,  $p=0.002$ ) and overall survival time was increased (48.9 [SD 1.46] days vs 53.65 [0.97] days, log-rank  $p=0.002$ ).

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

*Lancet Respir Med* 2015; 3: 943–52

Published Online  
November 17, 2015  
[http://dx.doi.org/10.1016/S2213-2600\(15\)00418-X](http://dx.doi.org/10.1016/S2213-2600(15)00418-X)

See [Comment](#) page 904

\*see appendix for the full list of investigators

**Northern Clinical School Intensive Care Research Unit** (G S Doig PhD, F Simpson PhD, P T Heighes MNE), and **The Boden Institute of Obesity, Nutrition Exercise, and Eating Disorders** (Prof I D Caterson FRAACP), University of Sydney, Sydney, NSW, Australia; **School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof R Bellomo MD); **New South Wales Health, Pathology, Sydney, NSW, Australia** (D Chesher PhD); **Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, QLD, Australia** (Prof M C Reade DPhil); and **John Hunter Hospital, New Lambton Heights, NSW,**



# Lancet, Respiratory Medicine

## Journal Style Sheet

## Background:

## Introduction

## Findings:

## Results:

## Interpretation:

## Conclusions:

### Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial



Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter W J Harrigan, for the Refeeding Syndrome Trial Investigators Group\*

#### Summary

**Background** Equipose exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

**Methods** We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration ( $>0.32$  mmol/L vs  $\leq 0.32$  mmol/L) and body-mass index (BMI;  $>18$  kg/m<sup>2</sup> vs  $\leq 18$  kg/m<sup>2</sup>). The primary outcome was the number of days alive after ICU discharge, with 60 day follow-up, in a modified intention-to-treat population of all randomly allocated patients except those mistakenly enrolled. Days alive after ICU discharge was a composite outcome based on ICU length of stay, overall survival time, and mortality. The Refeeding Syndrome Trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR number 12609001043224).

**Findings** Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39.9 (95% CI 36.4–43.7) compared with 44.8 (95% CI 40.9–49.1) in 166 assessable patients in the caloric restriction group (difference 4.9 days, 95% CI –2.3 to 13.6,  $p=0.19$ ). Nevertheless, protocolised caloric restriction improved key individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 vs 149 [91%] of 164,  $p=0.002$ ) and overall survival time was increased (48.9 [SD 1.46] days vs 53.65 [0.97] days, log-rank  $p=0.002$ ).

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

*Lancet Respir Med* 2015; 3: 943–52

Published Online  
November 17, 2015  
[http://dx.doi.org/10.1016/S2213-2600\(15\)00418-X](http://dx.doi.org/10.1016/S2213-2600(15)00418-X)

See [Comment](#) page 904

\*see appendix for the full list of investigators

**Northern Clinical School Intensive Care Research Unit** (G S Doig PhD, F Simpson PhD, P T Heighes MNE), and **The Boden Institute of Obesity, Nutrition Exercise, and Eating Disorders** (Prof I D Caterson FRA CP), **University of Sydney, Sydney, NSW, Australia**; **School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof R Bellomo MD); **New South Wales Health, Pathology, Sydney, NSW, Australia** (D Chesher PhD); **Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, QLD, Australia** (Prof M C Reade DPhil); and **John Hunter Hospital, New Lambton Heights, NSW,**



# Lancet, Respiratory Medicine

## Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial



Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter W J Harrigan, for the Refeeding Syndrome Trial Investigators Group\*

### Summary

**Background** Equipoise exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

**Methods** We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration ( $>0.32$  mmol/L vs  $\leq 0.32$  mmol/L) and body-mass index (BMI;  $>18$  kg/m<sup>2</sup> vs  $\leq 18$  kg/m<sup>2</sup>). The primary outcome was the number of days alive after ICU discharge, with 60 day follow-up, in a modified intention-to-treat population of all randomly allocated patients except those mistakenly enrolled. Days alive after ICU discharge was a composite outcome based on ICU length of stay, overall survival time, and mortality. The Refeeding Syndrome Trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR number 12609001043224).

**Findings** Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39.9 (95% CI 36.4–43.7) compared with 44.8 (95% CI 40.9–49.1) in 166 assessable patients in the caloric restriction group (difference 4.9 days, 95% CI –2.3 to 13.6,  $p=0.19$ ). Nevertheless, protocolised caloric restriction improved key individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 vs 149 [91%] of 164,  $p=0.002$ ) and overall survival time was increased (48.9 [SD 1.46] days vs 53.65 [0.97] days, log-rank  $p=0.002$ ).

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

*Lancet Respir Med* 2015; 3: 943–52

Published Online  
November 17, 2015  
[http://dx.doi.org/10.1016/S2213-2600\(15\)00418-X](http://dx.doi.org/10.1016/S2213-2600(15)00418-X)

See [Comment](#) page 904

\*see appendix for the full list of investigators

**Northern Clinical School Intensive Care Research Unit** (G S Doig PhD, F Simpson PhD, P T Heighes MNE), and **The Boden Institute of Obesity, Nutrition Exercise, and Eating Disorders** (Prof I D Caterson FRA CP), University of Sydney, Sydney, NSW, Australia; **School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof R Bellomo MD); **New South Wales Health, Pathology, Sydney, NSW, Australia** (D Chesher PhD); **Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, QLD, Australia** (Prof M C Reade DPhil); and **John Hunter Hospital, New Lambton Heights, NSW,**



# Lancet, Respiratory Medicine

## Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial



Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter WJ Harrigan, for the Refeeding Syndrome Trial Investigators Group\*

### Summary

**Background** Equipose exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

**Methods** We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration ( $>0.32$  mmol/L vs  $\leq 0.32$  mmol/L) and body-mass index (BMI;  $>18$  kg/m<sup>2</sup> vs  $\leq 18$  kg/m<sup>2</sup>). The primary outcome was the number of days alive after ICU discharge,

*Lancet Respir Med* 2015; 3: 943-52

Published Online  
November 17, 2015  
[http://dx.doi.org/10.1016/S2213-2600\(15\)00418-X](http://dx.doi.org/10.1016/S2213-2600(15)00418-X)

See [Comment](#) page 904

\*see appendix for the full list of investigators

Northern Clinical School  
Intensive Care Research Unit  
(G S Doig PhD, F Simpson PhD,  
D T Heighes MBE, and The

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

**Findings** Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39.9 (95% CI 36.4-43.7) compared with 44.8 (95% CI 40.9-49.1) in 166 assessable patients in the caloric restriction group (difference 4.9 days, 95% CI -2.3 to 13.6,  $p=0.19$ ). Nevertheless, protocolised caloric restriction improved key individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 vs 149 [91%] of 164,  $p=0.002$ ) and overall survival time was increased (48.9 [SD 1.46] days vs 53.65 [0.97] days, log-rank  $p=0.002$ ).

Public Health and Preventive  
Medicine, Monash University,  
Melbourne, VIC, Australia  
(Prof R Bellomo MD); New  
South Wales Health, Pathology,  
Sydney, NSW, Australia  
(D Chesher PhD); Burns, Trauma  
and Critical Care Research  
Centre, University of  
Queensland, Brisbane, QLD,  
Australia (Prof M C Reade DPhil);  
and John Hunter Hospital, New  
Lambton Heights, NSW,

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.





# Lancet, Respiratory Medicine

## Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial



Gordon S Doig, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter WJ Harrigan, for the Refeeding Syndrome Trial Investigators Group\*

### Summary

**Background** Equipose exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

**Methods** We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration ( $>0.32$  mmol/L vs  $\leq 0.32$  mmol/L) and body-mass index (BMI;  $>18$  kg/m<sup>2</sup> vs  $\leq 18$  kg/m<sup>2</sup>). The primary outcome was the number of days alive after ICU discharge,

*Lancet Respir Med* 2015; 3: 943-52

Published Online  
November 17, 2015  
[http://dx.doi.org/10.1016/S2213-2600\(15\)00418-X](http://dx.doi.org/10.1016/S2213-2600(15)00418-X)

See [Comment](#) page 904

\*see appendix for the full list of investigators

Northern Clinical School  
Intensive Care Research Unit  
(G S Doig PhD, F Simpson PhD,  
D T Heighes MBE, and The

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

**Findings** Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39.9 (95% CI 36.4-43.7) compared with 44.8 (95% CI 40.9-49.1) in 166 assessable patients in the caloric restriction group (difference 4.9 days, 95% CI -2.3 to 13.6,  $p=0.19$ ). Nevertheless, protocolised caloric restriction improved key individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 vs 149 [91%] of 164,  $p=0.002$ ) and overall survival time was increased (48.9 [SD 1.46] days vs 53.65 [0.97] days, log-rank  $p=0.002$ ).

Public Health and Preventive  
Medicine, Monash University,  
Melbourne, VIC, Australia  
(Prof R Bellomo MD); New  
South Wales Health, Pathology,  
Sydney, NSW, Australia  
(D Chesher PhD); Burns, Trauma  
and Critical Care Research  
Centre, University of  
Queensland, Brisbane, QLD,  
Australia (Prof M C Reade DPhil);  
and John Hunter Hospital, New  
Lambton Heights, NSW,

**Interpretation** Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.



## Avoiding rejection by Editor

*Editor determines content not appropriate for journal, content not interesting to journal, very bad study, **very poorly written**.*

Journal Editors are very busy.

- Carry a clinical load, have their own research programs, usually *not* paid as Editors.
- The *easiest* decision for a Editor to make is '**Reject without Review**'.
  - Immediately removes work from their inbox.
  - Reduces future work, as they will never see the paper again!

Because Editors are busy, there is only **one** section of your paper you can guarantee an Editor will read:

- It is usually the section we write last, when we are tired.
- We put the least effort into it, yet it might be the most important section.

**If your Abstract is poorly written, you make it easy for the Editor to 'Reject without Review'!**



## *Avoiding rejection by Reviewers*

---

348 of 1,038 papers sent by Editor to external reviewers

- **86%** (301/348) rejected after negative comments from reviewers
  - Reviewers determine bad study, poorly explained or poorly written.
  - *Sometimes* reviewers determine content not appropriate for journal or content not interesting to journal.
  - *Sometimes* reviewers recommend Reject after Authors fail to make recommended corrections!



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.**  
Sometimes determine content not appropriate for journal or content not  
interesting to journal. Sometimes reviewers recommend Reject after  
Authors fail to make recommended corrections!*



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.***

*Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after  
Authors fail to make recommended corrections!*

Reviewers are very busy.

- Carry a clinical load and have their own research programs.



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.** Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend **Reject** after **Authors fail to make recommended corrections!***

Reviewers are very busy.

- Carry a clinical load and have their own research programs.
- Reviewers cannot '**Reject without Review**'. They must read your whole paper but:



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.** Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend **Reject** after **Authors fail to make recommended corrections!***

Reviewers are very busy.

- Carry a clinical load and have their own research programs.
- Reviewers cannot '**Reject without Review**'. They must read your whole paper but:
  - If your **paper** is poorly written and difficult to understand, they will stop reading and recommend '**Reject**'!
  - If your paper is difficult to understand, Reviewers do not usually provide objective reasons for Rejection. They just send a Confidential Comment to the Editor recommending **Reject**.



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.**  
Sometimes determine content not appropriate for journal or content not  
interesting to journal. Sometimes reviewers recommend **Reject** after  
Authors fail to make recommended corrections!*

Reviewers are very busy.





## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.***

*Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after  
Authors fail to make recommended corrections!*

Reviewers are very busy.

- Make your papers *easy* to understand.



## *Avoiding rejection by Reviewers*

---

*Reviewers determine **bad study, poorly explained or poorly written.**  
Sometimes determine content not appropriate for journal or content not  
interesting to journal. Sometimes reviewers recommend **Reject** after  
**Authors fail to make recommended corrections!***

Reviewers are very busy.

- Make your papers *easy* to understand.
- Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.
  - Use these papers as a guide for journal selection and **study design.**
  - Use these papers as a guide for English language use.



## Avoiding rejection by Reviewers

Reviewers determine *bad study, poorly explained or poorly written*.  
Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after  
*Authors fail to make recommended corrections!*

Reviewers are very busy.

- Make your papers *easy* to understand.
- Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.
  - Use these papers as a guide for journal selection and **study design**.
  - Use these papers as a guide for English language use.
- Every journal has its own unique conventions.

**Interpretation** Protocolised caloric restriction **is a suitable therapeutic option** for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.



## Avoiding rejection by Reviewers

---

*Reviewers determine **bad study, poorly explained or poorly written.***  
*Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after*  
*Authors fail to make recommended corrections!*

Reviewers are very busy.

- Make your papers *easy* to understand.
- Identify a small number of candidate journals and retrieve 2 or 3 published papers from each.
  - Use these papers as a guide for journal selection and **study design.**
  - Use these papers as a guide for English language use.
- Every journal has its own unique conventions.
- **Conversational English is different to Scientific English.**
  - Have two translators: One who is good at conversational English and one who is a content area expert.



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written.*

*Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

Usually the Editor makes this decision before he/she sends your paper out for review.

The best way to address this issue is through good Journal selection before you submit your paper!



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!





## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers!



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers!

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers!

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.
  - You will always lose an argument with the Editor!



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers! **But you can Negotiate! Gently!**

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.
  - You will always lose an argument with the Editor!



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers! **But you can Negotiate! Gently!**

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.
  - You will always lose an argument with the Editor!

If a Reviewer wants 57 changes, and you disagree with all 57 requests:



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers! **But you can Negotiate! Gently!**

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.
  - You will always lose an argument with the Editor!

If a Reviewer wants 57 changes, and you disagree with all 57 requests:

- Make all 57 changes anyway or...



## *Avoiding rejection by Reviewers*

---

*Reviewers determine bad study, poorly explained or poorly written. Sometimes determine content not appropriate for journal or content not interesting to journal. Sometimes reviewers recommend Reject after Authors fail to make recommended corrections!*

If the Editor returns your paper and asks for Minor or Major Revisions based on Reviewers comments, **you are almost published!**

- 85% of submissions do not make it to this stage!

Do not argue with your Reviewers! **But you can Negotiate! Gently!**

- The Editor is often one of your Reviewers!!! So, if you choose to argue, you may be arguing with the Editor.
  - You will always lose an argument with the Editor!

If a Reviewer wants 57 changes, and you disagree with all 57 requests:

- Make all 57 changes anyway or...
- Make 55 changes.... and point out politely why you **can't** make the last 2 changes.



# *General Insights*

---

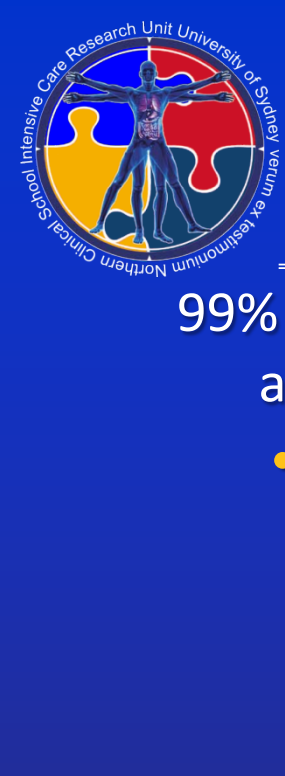




## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in *your* country.



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in *your* country.

- They do not understand the care you provide is just as good, or better, than the care they provide!



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in *your* country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in your country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.

- Admission APACHE for US journals / SAPS for European journals.



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in your country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.

- Admission APACHE for US journals / SAPS for European journals.

Describe routine care using statements to demonstrate you are familiar with best practice:



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in your country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.

- Admission APACHE for US journals / SAPS for European journals.

Describe routine care using statements to demonstrate you are familiar with best practice:

- “Nutrition support was provided in line with” SCCM guidelines (for US journals) / ESICM guidelines (for European journals).



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in your country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.

- Admission APACHE for US journals / SAPS for European journals.

Describe routine care using statements to demonstrate you are familiar with best practice:

- “Nutrition support was provided in line with” SCCM guidelines (for US journals) / ESICM guidelines (for European journals).
- “Patients with ARDs were ventilated using low tidal volumes (ref to US study) and prone (ref to French study) when required.”



## General Insights

---

99% of the Editors and Reviewers who read *your* paper have never been to an ICU in your country.

- They do not understand the care you provide is just as good, or better, than the care they provide!

Describe your patients and your ICU in terms they understand.

- Admission APACHE for US journals / SAPS for European journals.

Describe routine care using statements to demonstrate you are familiar with best practice:

- “Nutrition support was provided in line with” SCCM guidelines (for US journals) / ESICM guidelines (for European journals).
- “Patients with ARDs were ventilated using low tidal volumes (ref to US study) and prone (ref to French study) when required.”

If you use your *country name* in the title, the Editor or Reviewer may conclude your results apply only to your country and perhaps your paper is not interesting to their Journal!





# Summary

---



## *Summary*

---

63% (654/1,038) of papers are rejected by the Editor,



## Summary

---

63% (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.



## Summary

---

63% (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.



## Summary

---

63% (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!



## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected



## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.



## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.
  - Use successful publications to guide your data collection (APACHE/SAPS), study design, and use of English.





## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.
  - Use successful publications to guide your data collection (APACHE/SAPS), study design, and use of English.
- **Always** change your manuscript in response to Reviewer's comments



## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.
  - Use successful publications to guide your data collection (APACHE/SAPS), study design, and use of English.
- **Always** change your manuscript in response to Reviewer's comments

**Finally**, remember that only 8% (83/1,038) of submissions get Accepted.



## Summary

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.
  - Use successful publications to guide your data collection (APACHE/SAPS), study design, and use of English.
- **Always** change your manuscript in response to Reviewer's comments

**Finally**, remember that only 8% (83/1,038) of submissions get Accepted.

- Don't give up. ***Your research is important to your patients!***



## Questions??

---

**63%** (654/1,038) of papers are rejected by the Editor,

- Usually because the Editor determines your content is not appropriate for the Journal.
  - Select your target Journal **before** you start your Research.
  - Make sure your target Journal has published research projects similar to yours in the past.
- Remember, the Editor is busy. Make your **Abstract** easy to understand!

**86%** (301/348) of papers sent to Reviewers are rejected

- Usually because Reviewers disagree with what you have done or the way you present or interpret your data.
  - Use successful publications to guide your data collection (APACHE/SAPS), study design, and use of English.
- **Always** change your manuscript in response to Reviewer's comments

**Finally**, remember that only 8% (83/1,038) of submissions get Accepted.

- Don't give up. ***Your research is important to your patients!***