

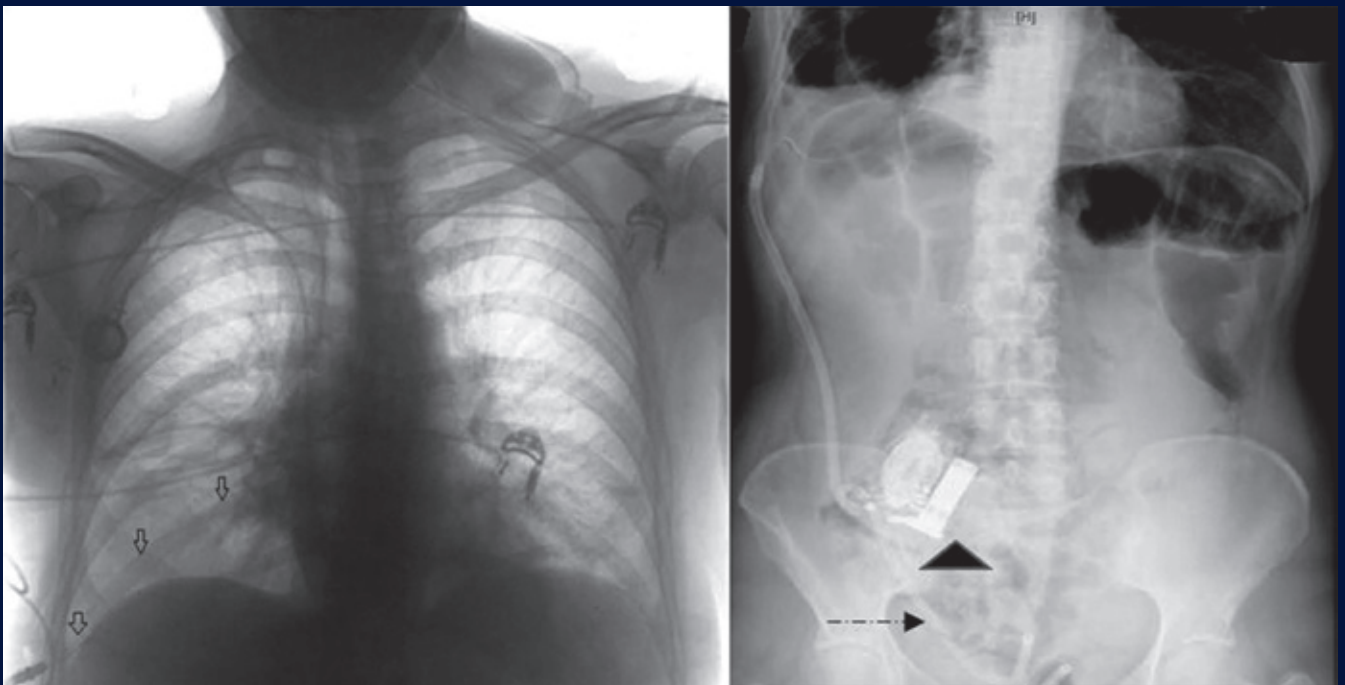
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa



thorax.bmj.com
adc.bmj.com



RCPCH
Royal College of
Paediatrics and Child Health
Leading the way in Children's Health

BMJ

1 VEZ DIA¹

xoterna[®]

breezhaler[®]

Indacaterol/glicopirrônio pó para inalação, cápsulas



Primeira associação fixa LAMA/LABA^{1*}

MELHORA OS SINTOMAS DE HOJE^{3**}...

... REDUZ FUTURAS EXACERBAÇÕES^{2,5#}

Estudo CRYSTAL³

117%

Melhoria da dispneia
vs LABA/ICS³

(Medida através do TDI.
Cálculo realizado a partir dos dados
de Melhoria do TDI do Estudo
CRYSTAL (Δ = 1,10 uds;
p<0,0001 às 12 semanas)

17%

de diminuição
na taxa de exacerbações
moderadas a graves

vs SFC²
(às 52 semanas) p<0,001

Estudo FLAME²

BREEZHALER, O DISPOSITIVO COM MENOR TAXA DE ERROS CRÍTICOS** ASSOCIADOS AO SEU USO⁴⁵

*Informação sobre medicamentos do INFARMED consultada em página da internet do sítio do Infarmed (acessada em 2020/01/15); ¹Indacaterol/glicopirrônio(110/50µg 1x dia) vs Salmeterol/Fluticasona(500/50µg 2x dia), glicopirrônio(50µg 1x dia) e tiotropio(18µg 1x dia); ²Melhoria da dispneia vs LABA/ICS³, LABA e LAMA avaliada através do TDI; ³Breezhaler vs restantes inaladores em estudo (Respimat[®], pMDI[®], Turbuhaler[®], Handihaler[®] e Diskus[®]); ⁴Erro crítico: aquele que pode afetar substancialmente a dose que chega ao pulmão; ⁵LAMA: Antagonista muscarínico de longa duração de ação; LABA: agonista B2 de longa ação; ICS: Corticosteroide Inalado; pMDI: inaladores pressurizados doseáveis; TDI: Transition Dyspnea Index; SFC: Salmeterol/Fluticasona 50/50µg 2x dia; Δ: diferença entre terapêuticas. 1. RCM XOTERNA[®] BREEZHALER[®] 05/2019; 2. Wedzicha JA, Banerji D, Chapman KR. Indacaterol/Glycopyrronium Versus Salmeterol/Fluticasone for COPD Exacerbations. New England Journal of Medicine. 2016;374:2222-2234; 3. Vogelmeier CF, Gaga M, Alamian-Mattheis M, Greulich T, Marin JM, Castellani W, et al. Efficacy and safety of direct switch to indacaterol/glycopyrronium patients with moderate COPD: the CRYSTAL open-label randomised trial. Respir Res. 2017 Jul 18;18(1):140; 4. Molimard M, Raheison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Respir J 2017; 49:1601794; 5. Wedzicha JA, Drecamer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209; ⁶População estudo FLAME: Doentes com DPOC com história de ≥1 exacerbações no ano prévio à inclusão.

Xoterna Breezhaler 85 microgramas/43 microgramas, pó para inalação, cápsulas (indacaterol/glicopirrônio) **Nota Importante:** Antes de prescrever consulte o Resumo das Características do Medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsulas contendo 143 microgramas de maleato de indacaterol equivalente a 110 microgramas de indacaterol e 63 microgramas de brometo de glicopirrônio equivalente a 50 microgramas de glicopirrônio. Cada dose libertada do aplicador bucal do inalador contém 110 microgramas de maleato de indacaterol equivalente a 85 microgramas de indacaterol e 54 microgramas de brometo de glicopirrônio equivalente a 43 microgramas de glicopirrônio. **INDICAÇÕES:** Xoterna Breezhaler é indicado como tratamento broncodilatador de manutenção para alívio dos sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). **POSOLOGIA E MODO DE ADMINISTRAÇÃO: Adultos:** A dose recomendada é a inalação do conteúdo de uma cápsula uma vez por dia, usando o inalador Xoterna Breezhaler. Deve ser utilizado o inalador fornecido com cada nova prescrição. **Populações especiais de doentes:** **Compromisso renal:** pode ser usado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal terminal que necessitem de diálise, este deve ser usado se o benefício esperado superar o risco potencial. **Compromisso hepático:** pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não estão disponíveis dados para a utilização em doentes com compromisso grave da função hepática. **População idosa:** pode ser utilizado na dose recomendada em doentes idosos (idade igual ou superior a 75 anos). **População pediátrica (<18 anos):** a segurança e eficácia não foram estabelecidas. Não existem dados disponíveis. **Modo de administração:** As cápsulas de Xoterna Breezhaler devem ser administradas pela via inalatória oral e apenas com a utilização do inalador Xoterna Breezhaler. As cápsulas não devem ser engolidas. Xoterna Breezhaler deve ser administrado à mesma hora do dia todos os dias. Se for omitida uma dose, esta deve ser tomada assim que possível no mesmo dia. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas devem ser sempre conservadas no blister de origem para proteger da humidade, e apenas retiradas imediatamente antes da utilização. Os doentes devem ser instruídos a administrar o medicamento corretamente. Os doentes que não sentiram melhorias na respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes de Xoterna Breezhaler. **ADVERTÊNCIAS/PRECAUÇÕES:** **• Xoterna Breezhaler não deve ser administrado concomitantemente com medicamentos contendo agonistas beta-adrenérgicos de longa duração ou antagonistas muscarínicos de longa duração** **• asma:** não deve ser usado no tratamento da asma, os agonistas beta-adrenérgicos de longa duração podem aumentar o risco de acontecimentos adversos graves relacionados com a asma, incluindo mortes relacionadas com a asma, quando utilizados no tratamento da asma **• utilização aguda:** não está indicado para o tratamento de episódios agudos de broncospasmos **• hipersensibilidade:** se ocorrerem reações de hipersensibilidade, em particular angioedema, urticária ou erupção cutânea, o tratamento com Xoterna Breezhaler deve ser descontinuado e deverá ser instituída terapêutica alternativa **• broncospasmos paradoxais:** administração de Xoterna Breezhaler pode resultar em broncospasmos paradoxais, o que pode pôr em risco a vida. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa **• efeitos anticolinérgicos relacionados com glicopirrônio:** utilizar com precaução em doentes com glaucoma de ângulo estreito e retenção urinária **• efeitos sistémicos de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, deve ser utilizado com precaução em doentes com perturbações cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão); em doentes com perturbações convulsivas ou tirotóxicose, e em doentes com resposta aumentada aos agonistas beta-adrenérgicos **• doentes com compromisso renal grave:** apenas deve ser utilizado se o benefício esperado superar o risco potencial em doentes com compromisso renal grave, incluindo os com doença renal terminal necessitando de diálise **• efeitos cardiovasculares de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, pode causar efeitos cardiovasculares clinicamente significativos em alguns doentes, evidenciados pelo aumento da frequência cardíaca, pressão arterial e/ou sintomas, alterações no eletrocardiograma (ECG) **• hipocalcémia:** os agonistas beta-adrenérgicos podem produzir hipocalcémia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. A diminuição do potássio sérico é usualmente transitória, não requerendo suplementação. Em doentes com DPOC grave, a hipocalcémia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas **• hiperglicémia:** A inalação de doses elevadas de agonistas beta-adrenérgicos pode produzir aumento da glicose plasmática. Ao iniciar o tratamento com Xoterna Breezhaler, a glicose plasmática deve ser monitorizada cuidadosamente em doentes diabéticos. Xoterna Breezhaler não foi estudado em doentes com diabetes mellitus inadequadamente controlada, portanto, é recomendada precaução e monitorização apropriada nestes doentes. **• Xoterna Breezhaler contém lactose.** Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou má absorção de glicose-galactose não devem tomar este medicamento. **GRAVIDEZ:** apenas deve ser usado durante a gravidez se os benefícios esperados para o doente compensarem os potenciais riscos para o feto. **TRABALHO DE PARTO: Informação relacionada com indacaterol** – tal como com outros medicamentos contendo agonistas beta-adrenérgicos, Xoterna Breezhaler pode inibir o trabalho de parto devido ao efeito relaxante no músculo liso uterino. **ALEITAMENTO:** apenas deve ser considerado se os benefícios esperados para a mulher compensarem qualquer potencial risco para a criança. **FERTILIDADE:** os estudos de reprodução e outros dados em animais não levantam preocupações no que respeita a fertilidade quer em machos quer em fêmeas. **INTERAÇÕES:** **• Não foram conduzidos estudos de interação específicos com Xoterna Breezhaler.** A informação sobre o potencial de interações é baseada no potencial para cada uma das suas duas substâncias ativas. **• não deve ser administrado conjuntamente com bloqueadores beta-adrenérgicos (incluindo colírios)** exceto se existirem razões imperiosas para a sua utilização **• os fármacos conhecidos por prolongar o intervalo QT podem aumentar o risco de arritmia ventricular** **• a administração concomitante de outros agentes simpaticomiméticos pode potenciar os efeitos indesejáveis** **• o tratamento concomitante com derivados da metilxantina, corticosteroides ou diuréticos não-poupará do potássio pode potenciar o possível efeito hipocalcémico dos agonistas beta-adrenérgicos** **• a inibição dos principais contribuidores para a depuração do indacaterol, GYP3A4 e glicoproteína P (P-gp) não tem impacto na segurança das doses terapêuticas** **• a coadministração com outros medicamentos que contêm anticolinérgicos não foi estudada e portanto não é recomendada** **• não se esperam interações medicamentosas relevantes quando glicopirrônio é coadministrado com cimetiídina ou outros inibidores do transporte de catião orgânicos.** **EFEITOS INDESEJÁVEIS:** O perfil de segurança é caracterizado por sintomas beta-adrenérgicos e anticolinérgicos típicos relacionados com os componentes individuais da associação. Outras reações adversas mais frequentes relacionadas com o medicamento foram tosse, nasofaringite e cefaleias. **Reações adversas de Xoterna Breezhaler:** **• Muito frequentes (≥1/10):** infeção do trato respiratório superior. **• Frequentes (≥1/100, <1/10):** nasofaringite, infeção do trato urinário, sinusite, rinite, hipersensibilidade, hiperglicémia e diabetes mellitus, tonturas, cefaleias, tosse, dor orofaríngea incluindo irritação da garganta, dispepsia, cáries dentárias, obstrução da bexiga e retenção urinária, priexia¹¹, dor torácica. **• Pouco frequentes (≥1/1.000, <1/100):** angioedema, insónia, glaucoma¹¹, doença cardíaca isquémica, fibrilhação atrial, taquicardia, palpitações, broncospasmos paradoxais, distonia, epistaxis, gastroenterite, xerostomia, prurido/eritema, dor musculoesquelética, espasmos musculares, mialgias, dor nas extremidades, edema periférico e fadiga. **• Raros (≥1/10.000, <1/1.000):** parestesias. ¹¹Reação adversa observada com Xoterna Breezhaler mas não com os componentes individuais. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** Novartis Europharm Limited. **REPRESENTANTE LOCAL:** Laboratório Medinfar-Produtos Farmacêuticos, S.A. Rua Henrique de Paiva Couceiro, N.º 29, Venda Nova, 2700-451 Amadora, Portugal. **Escalação de comparticipação:** B (69%). Medicamento sujeito a receita médica. Para mais informações deverá contactar o titular da AIM/representante local do titular da AIM. XOT_RCM201905_JEC_V09

Número verde: 800 204 661

LABORATÓRIO MEDINFAR - PRODUTOS FARMACÊUTICOS, S.A. | Rua Henrique Paiva Couceiro, n.º29, Venda Nova 2700-451 Amadora

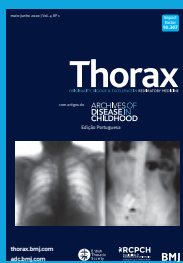
Tel. 21 499 74 00 | Fax. 21 499 74 97 | email: medinfar@medinfar.pt | www.medinfar.pt | Capital Social: €7.000.000,00 - Contribuinte n.º 500 384 045

Sob licença Novartis - Medicamento sujeito a receita médica. Para mais informações deverá contactar o titular da AIM/representante local do titular da AIM.

Xoterna Breezhaler-2020-01-FL-08 elaborado em janeiro de 2020

GRUPO
MEDINFAR

Há 50 anos a garantir o futuro



Journal of the British Thoracic Society
Impact Factor: 10.307

Editors-in-Chief

N Hart (UK)
G Jenkins (UK)
AR Smyth (UK)
Deputy Editor
R Chambers (UK)
C Wainwright (Australia)

Associate Editors

D Baldwin (UK)
HJ Bogaard
(The Netherlands)
S Christenson (USA)
T Coleman (UK)
A Condliffe (UK)
GJ Criner (USA)
J Davies (UK)
A Floto (UK)
M Griffiths (UK)
L Heaney (UK)
N Hopkinson (UK)
S James (UK)
DL Jarvis (UK)
B Kampman (UK)
O M Kon (UK)
B Mokhesi (USA)

I Noth (USA)
J-L Pepin (France)
M Polkey (UK)
J Quint (UK)
N Rahman (UK)
K Robinson (USA)
B Sage (UK)
R Stevens (USA)
T Wilkinson (UK)
P Wolters (USA)
C Bloom (UK)
L Donnelly (UK)
G Katsakos (UK)
W Lenney (UK)
C Scotton (UK)
P Wark (Australia)

Guidelines Associate Editor

I Du Rand (UK)
Statistical Editors
N Beckley-Hoelscher (UK)
A Douiri (UK)
C Flach (UK)
C Jackson (UK)
L Stanberry (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
B Wagner (USA)
Y Wang (UK)

Journal Club Editor

P Murphy (UK)

Multimedia Editor

R Moses (UK)

President, British Thoracic Society

Mohammed Munavvar
Editorial Office
Thorax, BMJ Journals, BMA House,
Tavistock Square, London, WC1H 9JR, UK
T: +44 (0)20 7383 6373
E: thorax@bmj.com

Twitter: @ThoraxBMJ

ISSN: 0040-6376 (print)

ISSN: 1468-3296 (online)

Disclaimer: Thorax is owned and published by the British Thoracic Society and BMJ Publishing Group Ltd, a wholly owned subsidiary of the British Medical Association. The owners grant editorial freedom to the Editor of Thorax. Thorax follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics.

Thorax is intended for medical professionals and is provided without warranty, express or implied. Statements in the Journal are the responsibility of their authors and advertisers and not authors' institutions, the BMJ Publishing Group Ltd, the British Thoracic Society or the BMA unless otherwise specified or determined by law. Acceptance of advertising does not imply endorsement. To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of Thorax or any information in it whether based on contract, tort or otherwise. Readers are advised to verify any information they choose to rely on.

Copyright: © 2020 BMJ Publishing Group Ltd and the British Thoracic Society. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of Thorax. Thorax is published by BMJ Publishing Group Ltd, typeset by Exeter Premedia Services Private Ltd, Chennai, India and printed in the UK on acid-free paper. Thorax (ISSN No: 0040-6376) is published monthly by BMJ Publishing Group and distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431. POSTMASTER: send address changes to Thorax, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY

Índice Volume 4 Número 1 Thorax com artigos do Archives of Disease in Childhood maio / junho 2020

Edição Portuguesa N.º 1 maio / junho 2020 - Volume 4

5 Editorial

7 Revisão

7 Se é “apenas” asma, porque é que ainda há crianças a morrer?

12 BTS Guideline

12 Orientação da *British Thoracic Society* para a utilização de macrólidos de longo prazo em adultos com doença respiratória

34 Epidemiologia respiratória

34 O índice de massa corporal e a alteração de peso estão associados a trajetórias da função pulmonar adultas: o estudo prospetivo ECRHS

40 Controvérsias e desafios na medicina respiratória

40 Defesa da continuidade de CPAP e VNI comunitárias durante a epidemia COVID-19
41 COVID-19: A CPAP e a VNI comunitárias devem ser interrompidas exceto se forem medicamente necessárias para suporte de vida

42 Comunicação curta

42 Gestão da bronquiólite grave: impacto das orientações NICE

45 Breve comunicação

45 Implementação do rastreio orientado de cancro do pulmão em população de risco elevado no âmbito da prática clínica no NHS através de tomografia computadorizada de dose reduzida



Thorax

com artigos do
**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa
Editada por:

Medjournal

Rua Bernardo Costa nº127, 1º Esquerdo
2775-809 Carcavelos
Contacto: 938311875
Email: geral@medjournal.pt
www.medjournal.pt
NIF: 510 542 719

General Manager
António Gonçalves

Diretores Médicos
Carlos Robalo Cordeiro
Jaime Correia de Sousa
Mário Morais de Almeida
Teresa Bandeira

A Medjournal não se responsabiliza pela opinião expressa dos autores.
Proibida a reprodução total ou parcial sob qualquer forma, sem autorização prévia do BMJ Publishing Group.



Editor in Chief

Nick Brown

Senior Editor

Rachel Agbeko

Deputy Editors

Patrick Cartledge (Commissioning)
Claire Lerner (Commissioning)
Ben Stenson (Fetal & Neonatal)
Ian Wacogne (Education & Practice)

Editorial Office

Archives of Disease in Childhood
BMJ Publishing Group Ltd
BMA House

Tavistock Square

London WC1H 9JR, UK

T: +44 (0)20 7383 6909

F: +44 (0)20 7383 6668

E: info.adc@bmj.com

Twitter: @ADC_BMJ

Production Editor

Malcolm Smith

E: production.adc@bmj.com

ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 3.158

Journal of the Royal College of

Paediatrics and Child Health

Disclaimer: ADC is published by BMJ Publishing Group Ltd (a wholly owned subsidiary of the British Medical Association) and the Royal College of Paediatrics and Child Health. The owners grant editorial freedom to the Editor of ADC. ADC follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics.

ADC is intended for medical professionals and is provided without warranty, express or implied. Statements in the journal are the responsibility of their authors and advertisers and not authors' institutions, the BMJ Publishing Group Ltd, the Royal College of Paediatrics and Child Health or the BMA unless otherwise specified or determined by law. Acceptance of advertising does not imply endorsement.

To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of ADC or any information in it whether based on contract, tort, or otherwise. Readers are advised to verify any information they choose to rely on.

Copyright © 2020 BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health.

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without prior permission. ADC is published by BMJ Publishing Group Ltd, typeset by Nova Techset Private Limited, Bengaluru & Chennai, India and printed in the UK on acid-free paper from sustainable forests. ADC (ISSN No: 0003-9888) is published monthly by BMJ Publishing Group Ltd and is distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431 and additional mailing offices. POSTMASTER: send address changes to Archives of Disease in Childhood, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA

Thorax

ORIGINALITY, RIGOUR AND EXCELLENCE
IN RESPIRATORY MEDICINE

Impact Factor: 10.307

Journal of the
British Thoracic Society

Editorial Board

H Aranibar (Chile)
R Beasley (New Zealand)
J Brown (UK)
J Celedon (USA)
T Fardon (UK)
P Gibson (Australia)
J Grigg (UK)
ML Han (USA)
F Holguin (USA)
N Kaminski (USA)
I Janahi (Qatar)
A Jones (UK)
A Knox (UK)
F Maltais (Canada)
D Mannino (USA)
S Nathan (USA)
I Pavord (UK)
F Ratjen (Canada)
J Scullion (UK)
J Simpson (UK)
M Steiner (UK)
A Torres (Spain)
Z Udwadia (India)
D Warburton (USA)
M Whyte (UK)

President, British Thoracic Society

Mohammed Munavvar

Publisher

Claire Rawlinson

Associate Publisher

Henry Spilberg

Guidelines for Authors and Reviewers

Full instructions are available online at <http://thorax.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/thorax>. Authors retain copyright but are required to grant *Thorax* an exclusive licence to publish <https://thorax.bmj.com/pages/authors/>

Aims and Scope: *Thorax* aims to cover all areas of respiratory medicine from paediatric to adults through publishing original papers, systematic reviews and meta-analyses, trial protocols, state of the art reviews, invited editorials, case-based discussions and images. The priorities are originality, rigour and excellence.

Editors-in-Chief

N Hart (UK)
G Jenkins (UK)
AR Smyth (UK)

Deputy Editors

R Chambers (UK)
C Wainwright (Australia)

Associate Editors

D Baldwin (UK)
HJ Bogaard (The Netherlands)
S Christenson (USA)
T Coleman (UK)
A Condliffe (UK)
GJ Criner (USA)
J Davies (UK)
A Floto (UK)
M Griffiths (UK)
L Heaney (UK)
N Hopkinson (UK)
S Janes (UK)
DL Jarvis (UK)
B Kampman (UK)
O M Kon (UK)
B Mokheles (USA)
I Noth (USA)
J-L Pepin (France)
M Polkey (UK)
J Quint (UK)
N Rahman (UK)

K Robinson (USA)
B Sage (UK)
R Stevens (USA)
T Wilkinson (UK)
P Wolters (USA)

C Bloom (UK)
L Donnelly (UK)
G Kaltsakas (UK)
W Lenney (UK)
C Scotton (UK)
P Wark (Australia)

Guidelines Associate Editor

I Du Rand (UK)

Statistical Editors

N Beckley-Hoelscher (UK)
A Douiri (UK)
C Flach (UK)
C Jackson (UK)
L Stanberry (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
B Wagner (USA)
Y Wang (UK)

Journal Club Editor

P Murphy (UK)

Multimedia Editor

R Moses (UK)

Contact Details

Editorial Office

Thorax, BMJ Journals, BMA House, Tavistock Square, London, WC1H 9JR, UK
E: thorax@bmj.com
Twitter: @ThoraxBMJ

British Thoracic Society

17 Doughty Street, London WC1N 2PL, UK
T: +44 (0)20 7831 8778
E: bts@brit-thoracic.org.uk
W: <https://www.brit-thoracic.org.uk/>

Customer Support

For general queries and support with subscriptions:
T: +44 (0)20 7111 1105
E: support@bmj.com
W: <https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and permissions

E: bmj.permissions@bmj.com
W: bmj.com/company/products-services/rights-and-licensing/

Advertising

W: bmj.com/company/for-advertisers-and-sponsor/

Display Advertising ROW

Sophie Fitzsimmons
T: +44 (0)20 3655 5612
E: sfzsimmons@bmj.com

Online Advertising ROW

Marc Clifford
T: +44 (0)20 3655 5610
E: mclifford@bmj.com

Display & Online Advertising Sales Americas

American Medical Communications (AMC)
T: +1 973 214 4374
E: rgordon@americanmedicalcomm.com

Author Reprints

BMJ Reprints Team
E: admin.reprints@bmj.com

Commercial Reprints ROW

Nadia Gurney-Randall
M: +44 (0)7866 262344
E: ngurneyrandall@bmj.com

Commercial Reprints Americas

Ray Thibodeau
T: +1 267 895 1758
M: +1 215 933 8484
E: ray.thibodeau@contentednet.com

Production Editor

Tasnia Nizam
E: production.thorax@bmj.com

For all other journal contacts:

<https://thorax.bmj.com/pages/contact-us/>

Subscription Information

Thorax is published monthly (subscribers receive all supplements)

Institutional Rates 2020

Print
£872

Online

Site licences are priced on FTE basis and allow access by the whole institution. Details available online at <http://www.bmj.com/company/bmj-for-institutions/> or contact Subscription (see above right).

Personal Rates 2020

Print (includes online access at no additional cost)
£368

Online only
£202

ISSN 0040-6376 (print)
ISSN 1468-3296 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <http://thorax.bmj.com/pages/subscribe/> (payment by (MasterCard/Visa only).

Residents of some EC countries must pay VAT; for details call us or visit <http://www.bmj.com/company/eu-vat-rates/>

Editorial

Estamos de volta com mais um número da edição em língua Portuguesa de artigos das Revistas *Thorax* e *Archives of Disease of Childhood*. Nesta edição selecionamos alguns artigos que esperamos sejam do vosso agrado. Informamos os nossos leitores que, por motivos editoriais, na presente e em futuras edições apenas serão traduzidos os títulos e os resumos dos artigos.

O primeiro artigo foca-se no artigo de revisão “*Se é “apenas” asma, porque é que ainda há crianças a morrer?*” que revisita a *National Review of Asthma Deaths* cinco anos depois e constata que os resultados em crianças com asma no Reino Unido continuam a estar abaixo dos resultados de outros países europeus. A presente revisão reporta os resultados de um estudo de entrevistas recente com 126 profissionais de saúde sobre o limiar de referência para clínicas especializadas em asma grave. Esta revisão proporciona uma definição operacional simples de asma grave com base nas atuais orientações nacionais e internacionais e descreve os benefícios potenciais do encaminhando atempado das crianças de alto risco para especialistas em asma grave.

O segundo destaque vai para a “Orientação da *British Thoracic Society* para a utilização de macrólidos de longo prazo em adultos com doença respiratória”. São detalhados os consensos da BTS em relação à utilização destes antibióticos em doentes específicos com asma, bronquiectasias, DPOC e bronquiolite obliterante.

Em seguida recomenda-se a leitura do artigo “O índice de massa corporal e a alteração de peso estão associados a trajetórias da função pulmonar adulta: o estudo prospetivo ECRHS”. Os autores procuraram estimar trajetórias de função pulmonar durante a idade adulta a partir de perfis de alteração de peso de 20 anos usando dados do estudo *European Community Respiratory Health Survey* (ECRHS) de base populacional incluindo 3673 participantes com idades entre 20 e 44 anos com medições repetidas de peso e função pulmonar. Os autores concluem que o aumento de peso moderado e elevado ao longo de 20 anos esteve associado à redução acelerada da função pulmonar, enquanto a perda de peso esteve relacionada com a sua atenuação. O controlo do aumento de peso é importante para a manutenção de uma boa função pulmonar na vida adulta.

Na secção de “Controvérsias e desafios na medicina respiratória” poderão ler duas cartas ao Editor sobre o uso de CPAP e VNI comunitárias durante a epidemia COVID-19. Na primeira carta os autores respondem aos autores da segunda e comentam que apesar de poder existir um risco potencialmente aumentado, embora desconhecido, de transmissão viral para outros elementos da família e prestadores de cuidados não se deve recomendar a interrupção genérica da utilização de CPAP. Contudo, se uma pessoa a fazer CPAP desenvolver sintomas compatíveis com COVID-19 ou for positivo mesmo que assintomático, parece sensato que interrompa a sua utilização por um período de cerca de duas semanas. Na segunda carta os autores apelam para a necessidade de uma opinião consensual sobre instruções mais claras para os pacientes e seus médicos, no interesse das famílias dos pacientes e dos seus cuidadores, sobre como isolar os doentes enquanto estiverem a usar VNI ou CPAP em casa, as disposições de segurança para os membros da família e a análise de risco-benefício da VNI temporária ou Cessação do CPAP.

O artigo seguinte, “Gestão da bronquiolite grave: impacto das orientações NICE” tem como objetivo compreender o impacto das orientações relativas à bronquiolite do *National Institute for Health and Care Excellence* (NICE) para a gestão de crianças referenciadas para unidades de cuidados intensivos pediátricos (UCIP) com bronquiolite. Os autores concluem que a utilização de nebulizador aumentou e observou-se um aumento da utilização de oxigénio por cânula nasal de fluxo elevado e uma redução da utilização da ventilação por pressão positiva contínua, isto apesar da orientação nacional em sentido contrário.

O último artigo avalia a “Implementação do rastreio orientado de cancro do pulmão em população de risco elevado no âmbito da prática clínica no NHS através de tomografia computadorizada de dose reduzida”. Os autores concluem que a abordagem tem sido implementada com sucesso na prática clínica de rotina e é eficaz em termos de melhorias de fase da doença e envolve indivíduos em áreas carenciadas.

Esperamos que a seleção de artigos vá ao encontro dos vossos interesses e desejamos uma boa leitura.

Editor in Chief

Nick Brown

Senior Editor

Rachel Agbeko

Deputy Editors

Patrick Cartledge (Commissioning)

Claire Lemer (Commissioning)

Ben Stenson (Fetal & Neonatal)

Ian Wacogne (Education & Practice)

Drug Therapy Editor

Dan Hawcutt

Global Child Health Editor

Trevor Duke

Health Policy Editor

John Puntis

Images Editor

Mark Tighe

Quality Improvement Editor

Claire Lemer

Adolescent Health Editor

Douglas Hargreaves

Social Media and Archimedes Editor

Bob Phillips

Archivist and Lucina Editor

Colin Powell

Voices Editor

Robert Scott-Jupp

Associate Editors

Karel Allegaert

Diana Baralle

Martin Bellman

Frances Bu'lock

Ronny Cheung

David Cottrell

Louise Fleming

Georgina Hall

Peter Hoyer

Fyezah Jehan

Stephanie L  r

Vic Larcher

Daniel Lumsden

Cynthia Mollen

Catherine Peters

Colin Powell

A V Ramanan

Andrew Riordan

Helen Sammons

Natasha Saunders

Robert Tasker

Paul Turner

Guidelines for Authors and Reviewers

Full instructions are available online at <https://adc.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/adc>. Authors retain copyright but are required to grant *ADC* an exclusive licence to publish (<https://adc.bmj.com/pages/authors/>)

Archives of Disease in Childhood focuses on all aspects of child health and disease from the perinatal period through adolescence

Statistical Editor

Tim Cole

Statistical Advisors

Emmanouil Bagkeris

Mario Cortina Borja

Sarah Donegan

Sara Godward

Marlous Hall

Katie Harron

Eirini Koutoumanou

Sarah Nevitt

Snehal Pinto Pereira

Deborah Ridout

Andrea Sherriff

Lesley Smith

Angie Wade

International Advisors

Zulfi A Bhutta

Leyla Namazova-Baranova

Education & Practice

Section Editors

Best practice

Ian Wacogne

Problem solving in clinical practice

Mark Anderson, Mark Tighe

Illuminations

Helen Williams

Dermatophile

Peter Lio

Interpretations

Sam Behjati, Thomas Waterfield

Epilogue

Mark Tighe, Lisa Brown

Guidelines

Philippa Prentice, Emma Dyer

Picket

Giordano Perez-Gaxiola,

Rebecca Dalrymple, Amanda Friend

Equipped and Equipment

Alice Roueche, Jane Runnacles

Public Health

Ronny Cheung

Research in Practice

Bob Phillips, John Apps

Medicines update

Emma McDonough, Louise Bracken



The Journal of the Royal College of Paediatrics and Child Health



ADC is the official journal of NPPG. NPPG members receive online access to *ADC* via the NPPG website.



Don't wait to read the latest *ADC* articles

Most articles accepted for publication in *ADC* are published online well before they appear in a print issue

- Read the latest articles by following the Online First link at the top right of the homepage (adc.bmj.com)
- Sign up for an email alert to be notified when new content is added (adc.bmj.com/cgi/alerts/etoc)
- Comment on the articles in the *ADC* Blog (<http://blogs.bmj.com/adc/>)

Subscription information

Archives of Disease in Childhood is published monthly plus *Fetal & Neonatal* Edition bimonthly and *Education & Practice* Edition bimonthly (subscribers receive all editions and supplements)

Institutional rates 2020

Print

£1036

Online

Site licences are priced on FTE basis and allow access by the whole institution. Print is available for online subscribers; details available online at <http://group.bmj.com/subscribe/?adc> or contact the Subscription Manager in the UK (see above right)

Personal rates 2020

Print (includes online access at no additional cost)

£475

Online only

£214

ISSN 0003-9888 (print); 1468-2044 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <https://adc.bmj.com/pages/subscribe/> (payment by Visa/Mastercard only)

Residents of some EC countries must pay VAT; for details, call us or visit support@bmj.com

Contact Details

Editorial Office

Archives of Disease in Childhood

BMJ Publishing Group Ltd

BMA House, Tavistock Square

London, WC1H 9JR, UK

E: info.adc@bmj.com

Customer Support

For general queries and support with existing and new subscriptions:

T: +44 (0)20 7111 1105

<https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and Permissions

W: bmj.com/company/products-services/rights-and-licensing/

E: bmj.permissions@bmj.com

Publisher

Christiane Notarmarco

Associate Publisher

Richard Sands

Publishing Executive

James Smallbone

E: jsmallbone@bmj.com

Senior Production Editor

Malcolm Smith

E: production.adc@bmj.com

Supplement enquiries

E: rsands@bmj.com

Subscriptions (except USA)

For all subscription enquiries and orders

T: +44 (0)20 7111 1105

<https://adc.bmj.com/pages/subscribe/>

Display Advertising Sales – Rest of World

Sophie Fitzsimmons

T: +44 (0)20 3655 5612

E: sfitzsimmons@bmj.com

<https://www.bmj.com/company/for-advertisers-and-sponsor/>

Online Advertising Sales

Marc Clifford

T: +44 (0)20 3655 5610

E: mclifford@bmj.com

<http://group.bmj.com/advertising/>

Display & Online Advertising Sales – North America

American Medical Communications (AMC)

T: +1 973 214 4374

E: rgordon@americanmedicalcomm

Se é “apenas” asma, porque é que ainda há crianças a morrer?

Will Carroll,^{1,2} Sadie Clayton,³ Susan Frost,⁴ Atul Gupta,⁵ Steve Holmes,⁶ Prasad Nagakumar,⁴ Mark Levy^{7,8}

¹Children's Respiratory Services, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

²Institute of Applied Clinical Sciences, Keele University, Keele, UK

³Child health, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

⁴Paediatric Respiratory Medicine and Cystic Fibrosis, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK

⁵Paediatric Respiratory Medicine, King's College London, London, UK

⁶Primary Care Respiratory Society UK, Park Medical Practice, Shepton Mallet, UK

⁷Clinical Lead for the UK National Review of Asthma Deaths (2011-4), London, UK

⁸Global Initiative on Asthma (GINA), Fontana, California, USA

Correspondence to

Dr Will Carroll, Children's Respiratory Services, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent ST4 6QG, UK; will.carroll@nhs.net

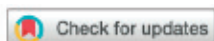
Received 10 September 2019

Revised 11 November 2019

Accepted 8 December 2019

Published Online First

23 December 2019



© Autor(es) (ou o(s) seu(s) empregador(es)) 2020. Não é permitida a utilização com fins comerciais. Consultar direitos e permissões. Publicado pela BMJ.

RESUMO

Os resultados de crianças com asma no Reino Unido continuam a estar abaixo dos resultados de outros países europeus. A mortalidade mantém-se inaceitavelmente elevada e, em contraste com os adultos com asma, a maioria das mortes ocorre na 1 em cada 20 crianças com asma que sofre de asma grave. Apesar da evidência de que as crianças com asma têm melhores resultados com cuidados de subespecialistas, muitas crianças com asma grave não lhes são referenciadas e existem barreiras em todos os níveis do sistema de cuidados de saúde do Reino Unido. A *National Review of Asthma Deaths* (NRAD) recomendou que a revisão por especialista deve ser requerida no caso de terem ocorrido 3 ou mais cursos de esteroides orais, duas ou mais visitas a unidades de urgência ou um internamento hospitalar. A presente revisão reporta os resultados de um estudo de entrevistas recente com 126 profissionais de saúde. Mais de metade dos clínicos gerais (n=49) reportaram que adotam um limiar mais elevado do que o mencionado. Os pediatras gerais (n=47) estabelecem um limiar ainda mais elevado. Os seus limiares medianos para uma referência para um subespecialista em asma foram de 4 cursos de esteroides orais, 3 internamentos hospitalares e 30 dias de absentismo escolar no ano anterior. Esta revisão proporciona uma definição operacional simples de asma grave com base nas atuais orientações nacionais e internacionais e fornece um exemplo dos critérios de referência recentemente adotados para clínicas de asma pediátrica grave nas West Midlands.

INTRODUCTION

In 2014 the National Review of Asthma Deaths (NRAD) carefully reviewed the care that had been received by individuals in the UK who had died from asthma. It highlighted the need for improvements, particularly in the care of children and young people (CYP) aged 0–19 years with asthma. The review concluded that there were potentially avoidable factors in 27 out of 28 of the cases involving CYP for whom records were available.¹ Worryingly, despite NRAD being a confidential enquiry, the records for a further eight CYP who died from asthma in the year of the study were not returned by their doctors.²

NRAD also highlighted an apparent complacency in the care of young people with asthma. Poor recognition of the risk status was found to be an important avoidable factor in 78% (22/28) of and in almost a third (5/16) of the CYP in primary and secondary care respectively.¹

In summarising the NRAD findings 5 years later, Asthma UK highlighted the ongoing poor quality of care for children with asthma in the UK. Aspects of care were well below the expected standard for about a quarter of the cases reviewed and almost half of CYP.³ This report should have been a ‘wake-up call’ to everyone caring for CYP with asthma in the UK. However, preventable asthma deaths in CYP have continued unabated and this has led to calls for national action to fully implement the NRAD recommendations.^{4,5}

What is already known?

- The UK has the highest rate of asthma deaths for children and young people (CYP) aged 10–24 years in Europe.
- A confidential review of asthma deaths in 2014 identified avoidable factors in almost all cases involving CYP.
- Asthma outcomes are better in adults and children who have specialist care.

What is already known?

- This commentary summarises the advice from available national and international asthma guidelines highlighting where evidence exists.
- It presents new data on how self-reported thresholds for referral in primary and secondary care deviate from existing guidelines.
- It describes the potential benefits of referring high risk children for specialist care.

The recently published (2019) Nuffield Report found that the UK still has the highest asthma mortality rate among young people aged 10–24 in the European countries included in the comparison. The asthma mortality rate for the UK was approximately twice as high as that of the next worst European country.⁶ This is despite access to numerous evidence-based guidelines and treatment options.^{7,8}

WHY ARE WE LETTING CHILDREN DOWN SO BADLY?

Several factors could account for these poor outcomes. These include a significant variability in the quality of healthcare provided,¹ failure to make a diagnosis of asthma or subsequently recognise risk of poor outcome or to implement national guidelines. Recent coronial reviews have also identified a lack of continuity of care with failure of one person taking overall responsibility for CYP with severe or difficult to treat asthma with some CYP suffering from a lack of basic care provision,³ coupled with a poor understanding of symptoms by CYP, parents and healthcare providers.^{9,10} Three separate Coroner's Regulation 28 notices concerning asthma deaths in CYP have been issued in the last 4 years.¹¹

Children are not just little adults. Asthma in children is not the same as adult asthma.¹² In contrast to adults, where deaths occur across all severities and more than half (58%) occur in individuals with mild or moderate asthma, deaths in children are most common in those with severe asthma with more than half (58%) of deaths in CYP occurring in this group.² While population estimates vary severe

Para citar: Carroll W, Clayton S, Frost S, et al. Arch Dis Child 2020;105:494–498.

Box 1 Working definition of severe asthma in children and young adults*

Confirmed asthma diagnosis with: optimised treatment

- ▶ Higher dose inhaled corticosteroid (≥ 800 μg beclomethasone dipropionate (BDP) equivalent daily for children 6–12 years, ≥ 1600 μg BDP equivalent daily for children >12 years).
 - ▶ $\pm$ long-acting beta-2 agonist, $\pm$ leukotriene receptor antagonist (if appropriate).
 - ▶ Adherence and inhaler technique checked and verified.
- AND

uncontrolled symptoms

- ▶ Assessed using childhood asthma control test (c-ACT) (children 4–11) and ACT (children ≥ 12). Asthma control questionnaire or similar could also be used.

OR

asthma attacks

- ▶ ≥ 2 courses of oral corticosteroids for three or more days in the last 12 months.
- ▶ Any hospital admission for asthma attack in the last 12 months.
- ▶ Any previous paediatric intensive care unit (PICU) admission or mechanical ventilation ever.

*Definition based on combination of Global Initiative for Asthma guidelines 2019, Scottish Intercollegiate Guidelines Network/British Thoracic Society guidelines 2019 for treatment of asthma and international European Respiratory Society/American Thoracic Society guidelines on definition, evaluation and treatment of severe asthma 2014.

asthma is likely to occur in 5% or less of CYP with asthma.^{13–15} Studies show that subspecialist care is associated with improved outcomes¹⁶ for CYP with asthma. However, the observational evidence from NRAD and population studies show that a significant proportion of CYP with persistent poor control are not referred onwards, with barriers existing between primary, secondary and tertiary care.¹⁷ There is now a body of evidence summarised in the new Global Initiative for Asthma (GINA) strategy document that individuals with ‘so called’ mild asthma are also at risk of poor outcomes. This is largely due to the adverse effects of regular use of short-acting beta-2 agonists (SABAs) and insufficient prescription of or adherence to inhaled corticosteroids (ICS) which has resulted in fundamental changes to the international recommendations for the treatment of asthma.^{6 18}

WHAT IS SEVERE ASTHMA?

Part of the problem that exists is that there is variation in the definition of severe asthma which is currently defined retrospectively based on the amount of treatment required to maintain control (see box 1).^{7 19}

CYP with poor symptom control despite being prescribed high dose asthma medication do not always have severe asthma. Some have alternate diagnoses and others will have modifiable factors

such as non-adherence. These individuals have difficult asthma.^{7,19} Difficult asthma is at least twice as common as severe asthma.¹³ While severe asthma currently accounts for up to 50% of asthma-related healthcare costs²⁰ the treatment landscape for CYP with severe asthma is changing as newer drugs become available.¹⁵

IT IS NOT JUST ADULTS WHO ARE SLIPPING THROUGH THE NET

A recent interview study involving 219 healthcare professionals in the UK revealed that referral thresholds for CYP with asthma remain high.²¹ The results of self-reported referral thresholds for participants in primary (n=79) and non-subspecialist secondary-care clinicians (n=47) are summarised in table 1. The results are remarkably similar to those seen in the recent asthma UK report ‘Slipping through the net’ which described the experience of healthcare professionals working in adult asthma services.²² Primary care healthcare professionals (General Practitioners (GPs and asthma nurses) report referring on to secondary care clinics (general paediatricians) when CYP with asthma have received a median of three courses of oral steroids, or had two Accident and Emergency (A&E) attendances or when a CYP has had 21 days off school in a year. Once in secondary care and under the care of a general paediatrician the referral thresholds to tertiary services (specialist difficult asthma clinics) are even higher; with children needing to have a median of four asthma attacks, four courses of oral steroids, three A&E attendances or hospital admissions, or more than 30 days off school in a single year before being referred. Moreover, a significant proportion of generalists reported uncertainty about what the referral threshold should be. An inquest in the matter of the preventable asthma death of a 10-year-old girl heard that despite having 48 attacks, including 10 with life threatening features, she was never referred to a respiratory paediatrician.¹¹

More than half of GPs and almost three-quarters of general paediatricians who answered self-reported adopting a higher threshold than the recommendations of NRAD which suggested specialist review if there had been three or more courses of oral steroids, two or more visits to accident and emergency or an admission to hospital.¹ A delayed specialist referral pathway is not simply putting CYP with severe asthma at increased risk. Caring for people who experience an asthma attack costs over 3.5 times more than for those whose asthma is well managed, and the estimated annual cost of treating a child with asthma is higher than the cost for an adult. In 2007–2008, 38% of emergency admissions for asthma were children aged under 15 and admissions per head of population were over twice as high for children as for adults.²³ Most importantly, many newer treatments are only available to children who are seen in specialist clinics.²⁴

Children, parents and healthcare providers seem to be willing to accept this situation, consistently reporting suboptimal control in population studies.^{9 25 26} It is disappointing that, despite access to high quality asthma guidelines, education and treatments, children’s asthma care remains so poor in the UK.⁶

WHAT CAN WE DO ABOUT IT?

These data confirm that risk is often poorly assessed and managed in CYP with asthma. Reliance on relievers and reluctance to use preventer inhalers regularly is a particularly important warning sign and this should be reviewed when a prescription is issued and discussed at every opportunity.

The evidence suggests that we should adopt a zero tolerance approach to asthma attacks, which have previously often been referred to as exacerbations. The word ‘attack’ helps to emphasise that asthma

Table 1 Self-reported thresholds for referral onwards of healthcare professionals (all values reported as medians (IQR))

Number in year before referral?	Attacks	Courses or oral steroids	A&E attendances	Hospital admissions	Days off school
Primary care (n=79)	3 (2)	3 (2)	2 (1)	1 (1)	15 (12)
GPs (n=49)	4 (2)	3 (2)	2 (1)	2 (1)	18 (15)
‘Not sure’(n (%))	7 (14)	9 (18)	7 (14)	4 (8)	20 (41)
Practice nurses (n=30)	2 (1)	3 (1)	2 (1)	1 (1)	15 (12)
‘Not sure’(n (%))	4 (13)	3 (10)	2 (6)	3 (10)	10 (38)
General paediatricians (n=47)	4 (1)	4 (1)	3 (1)	3 (2)	30 (21)
‘Not sure’(n (%))	9 (19)	8 (17)	14 (30)	9 (19)	18 (38)

Box 2 When to refer to specialist care (red flags for referral)*

Any child presenting to secondary care with a diagnosis of severe or difficult-to-treat asthma or who has

- ▶ Had ≥ 2 courses of oral corticosteroids (OCS) for three or more days in the last 12 months.

OR

- ▶ Had more than one hospital admission (inpatient or A&E) in the last 12 months.

OR

- ▶ Ever had a PICU admission requiring ventilatory support (mechanical/non-invasive).

OR

- ▶ Persistent poor control or unclear diagnosis for ≥ 3 months.

OR

- ▶ Has a requirement for long-term (≥ 1 month) OCS maintenance therapy.

OR

- ▶ Has other factors that increase the risk of death from asthma for example,
 - IgE mediated food allergy anaphylaxis.
 - Heavy use of short-acting beta-2 agonist (≥ 1 canister/200 doses per month).
 - Adverse behavioural or psychosocial factors

*Definition based on Global Initiative for Asthma guidelines 2019 and Scottish Intercollegiate Guidelines Network/British Thoracic Society 2019 guidelines for treatment of asthma

attacks are not acceptable or 'to be expected'. They are a signal that something serious has gone wrong and should always be followed up and investigated.¹ A recent large population survey using general practice records showed that less than 6% of UK children aged 12–17 years had an asthma attack in a 12-month period.²⁷ Subsequent assessment in primary or secondary care should include a careful review of treatment (particularly excess SABA and insufficient ICS prescriptions), inhaler technique, adherence, asthma control and lung function (in those old enough to perform it).^{1,7,8} Risk of hospitalisation increases significantly with SABA use once CYP use more than three canisters (600 doses) of SABA per year (OR 1.7 95%CI (1.1 to 2.4)). Use of more than 12 canisters per year is associated with a very significant increased risk of hospital admission for CYP asthma (OR 4.1 95%CI (2.0 to 8.3)).²⁸ CYP who are then found to have difficult to treat or severe asthma (see box 1) should be referred to a subspecialist or severe asthma service.^{17,19} The available national and international guidelines all have slightly different definitions of what constitutes severe asthma in CYP, however all agree that severe asthma only exists when there is a confirmed diagnosis of asthma and the symptoms or attacks persist despite optimised treatment (see box 1 for the definition used by the two paediatric asthma centres in the Midlands).

HOW SHOULD SEVERE ASTHMA BE MANAGED IN CYP?

CYP with poor asthma control are at increased risk for asthma attacks and death,^{1,29} and if severe may be eligible for treatment with newer biological agents. In many cases, asthma control can be improved by addressing adherence issues, by increasing the treatment offered or reducing exposure to triggers.⁸ This can be done in any setting but requires training, time and tenacity. Recent international guidance stresses the importance of referral to specialist care in individuals who continue to have asthma attacks or whose asthma symptoms persist despite higher treatment levels (see box 2).⁷

In the UK, the definition of an asthma specialist is rather blurred. This lack of clarity has some benefits but many perils. Anyone can declare themselves an asthma specialist, irrespective of training and resources, and this must cease if outcomes for children are to

be optimised. In some centres, this role has been fulfilled by general paediatricians with an interest in respiratory disease. Many referrals from primary care to a paediatric department will assume the patient has been picked up by a paediatrician with a more specialist interest. However, only a small proportion of paediatricians have access to the full range of multidisciplinary expertise, investigations and treatments that are required to both diagnose and treat severe asthma. This includes access to dedicated asthma nurses, adherence monitors eg, Smarthalers devices or similar, lung function testing including spirometry and fractional exhaled nitric oxide measures, flexible bronchoscopy, cardiopulmonary exercise testing, specialised imaging as well as having an understanding of and access to newer biologic agents. The GINA 2019 booklet on severe and difficult to treat asthma provides guidance at all levels of care for diagnosing and managing these individuals.⁶ The ability of the asthma nurse specialist to perform a home visit is also considered vital³⁰ (see box 3) as is access to a dedicated multi-disciplinary team.

LEARNING FROM RECENT EXPERIENCE IN ADULTS WITH SEVERE ASTHMA

There is strong emerging evidence that adults with severe asthma do better when seen and assessed in severe asthma centres. In the Netherlands, a single day review has been shown to have a long-term impact on asthma control, quality of life and healthcare utilisation.³¹ The emergence of newer technologies for measuring adherence and the advent of biological therapies for those who remain poorly controlled have been incorporated into the new NHS England guidance for adult asthma services.^{24,32}

Adults with severe asthma now benefit from the expertise of severe asthma centres.^{32,33} These have been developed using a 'hub and spoke' model, with care being coordinated from a central hub. This has significantly improved access to specialist support and to emerging and novel therapeutics for adults with severe asthma. National data are not available, however in the North West alone, the adult severe asthma hub has recommended initiation of biologics in 790 adults with severe asthma between 2015 and 2018 which are now licensed for use in children.¹⁵

Without changes in behaviour from primary and secondary care, CYP with asthma will be denied the same opportunities. suggested ReFeRRAL pATHWay While one size will never fit all, pathways for referral and good practice guides have been developed for use in the UK.³⁴ An example of one is given in figure 1 (below). This can be used to guide referrals. Nonetheless, there may be circumstances where referral is merited 'off pathway' before all criteria are fulfilled, for instance when diagnostic doubt exists and/or when there have been life-threatening events such as paediatric intensive care admission.

Box 3 proposed requirements for children and young people severe asthma service

A specialist multidisciplinary paediatric asthma service that has:

- ▶ At least two respiratory paediatricians with specific asthma training and expertise.
- ▶ Asthma nurse specialist(s). And direct access to other specialty services, such as:
 - ▶ Flexible bronchoscopy.
 - ▶ Lung function lab with certified spirometry specialists.
 - ▶ Lung physiology.
 - ▶ Physiotherapy.
 - ▶ Pharmacist.
 - ▶ Clinical psychologist.
 - ▶ Mental health services.
 - ▶ Social worker/safe guarding lead.
 - ▶ Ear, nose and throat specialist (ENT).
 - ▶ Speech and language therapy.

ADVICE FOR REFERRING TEAMS

When referring to a specialist multidisciplinary team it is useful to include as much information about the child and any test results or treatments they may have received as possible. This can include date of confirmed asthma diagnosis, confirmation of adherence and inhaler technique checks, current treatments and doses, copies from records of all asthma prescriptions issued in the previous 12 months, results from any tests performed for example, lung function (spirometry, best annual PEFR, fractional excretion of nitric oxide), skin prick or serum eosinophil count, any social/safeguarding concerns (such as not being brought for review in practice or hospital) or family history that should be taken into consideration and any comorbidities that are present.

It could also involve relevant historic medication prescribed print outs, previous hospital admission and A&E correspondence, and information relating to family and carer belief systems relating to asthma and the medications used.

CONCLUSION

The Nuffield report has provided us with a stark reminder, 5 years after NRAD, that the UK still has much more to do to improve the care of CYP with severe asthma. All too often asthma attacks in children are treated as isolated acute incidents by a variety of different healthcare professionals in different settings including paediatric emergency departments and out of hours services. Referral to specialist multidisciplinary care recognises and addresses the chronic nature of the disease and ensures the consistency of care that these children deserve.

Conflicting guidelines and a lack of clear referral pathways for CYP with severe asthma mean we are destined to repeat our failures. These result in significant delays in referral which must be overcome if we are to tackle the poor outcomes seen for UK children with asthma.

Acknowledgements The content was developed by the expert steering committee who have reviewed and take responsibility for the content. Development of this article was funded by Novartis Pharmaceuticals UK limited (Novartis) who supplied and paid for editorial assistance. The document was reviewed by Novartis for compliance with the ABPI code of Practice, final editorial control remained with the expert steering committee.

Contributors The original outline plan for the manuscript was developed by all authors. The initial draft manuscript was prepared by WC and this was circulated to all authors who provided references and additional content. Editorial assistance and manuscript preparation was then undertaken by a medical writer before a final draft was circulated for further comment of all authors. The raw data concerning referral thresholds for healthcare professionals in primary and secondary care was provided by Novartis Pharmaceuticals, who also paid for the services of the medical writer. The paper was reviewed by Dr Adam Strong of Novartis prior to submission to ensure that it was compliant with ABPI regulations.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests WC reports personal fees for lecturing and advisory board work from: GlaxoSmithKline, Trudell Medical International, Orion Medical and Novartis Pharmaceuticals. SC has received funding from Astra Zeneca, GlaxoSmithKline, Napp, Novartis, Teva and Circassia. SF has received funding from Novartis and is co-treasurer of the Severe Asthma Nurses Network which organises conferences for professional development. AG reports fees for lecturing/advisory board work from: GlaxoSmithKline, Novartis Pharmaceuticals, Boehringer Ingelheim and Astra Zeneca. He has been CI/PI of the clinical trials with GlaxoSmithKline, Novartis Pharmaceuticals, Boehringer Ingelheim, & Airosnott for which his institution has been paid. He is also a director of the non-profit organisation Paediatric Respiratory Academy which organises educational meetings. SH works as a GP, he is funded for 1/2 session per week as a clinical commissioner, has received funding from Astra Zeneca, Beximco, Boehringer Ingelheim, Chiesi, Glaxo Smith Kline, Johnson and Johnson, Mylan, Napp, Novartis, Nutricia, Orion, Pfizer, Sandoz, Teva and Trudell Medical International. PN has received funding from Novartis. ML reports personal fees from: Clement Clarke International, Teva, Astra Zeneca, Chiesi, Orion Pharmaceuticals, Napp Pharmaceuticals, Soar Beyond, Trudell Pharmaceuticals, National Services for Health Improvement, a company providing services for practices (Nurse Asthma Reviews), Novartis Pharmaceuticals, GlaxoSmithKline, reimbursement of travel and accommodation support from GINA, grants from Conzorcio Futuro In Ricerca, personal fees from, non-financial support from Asthma and COPD (Joint) Lead for Whole Systems Integrated Care (WSIC) NorthWest London.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Mark Levy 0000-0002-1807-3246

REFERENCES

- Why asthma still kills. The National review of asthma deaths (NRAD). confidential enquiry report, may 2014.
- Levy ML. The National review of asthma deaths: what did we learn and what needs to change? *Breathe* 2015;11:14–24.
- Asthma UK Briefing. The UK national review of asthma deaths, 2014. Available: <https://www.asthma.org.uk/290c82e/globalassets/campaigns/nrad-summary.pdf> [Accessed June 2019].
- Dyer C. Coroner calls for national policy for managing asthma after death of 10 year old. *BMJ* 2019;365:4038.
- Levy ML, Fleming L, Warner JO, et al. Paediatric asthma care in the UK: fragmented and fatally fallible. *Br J Gen Pract* 2019;69:405–6.
- Shah R, Haggall A, Cheung R. International comparisons of health and wellbeing in adolescence and early adulthood. Research report February 2019. Nuffield Trust in association with Association for Young People's Health. Available: http://www.youngpeopleshealth.org.uk/wp-content/uploads/2019/02/NF-AYPH-adolescenthealth-report_WEB-200219.pdf [Accessed June 2019].
- Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. Available: www.ginasthma.org [Accessed June 2019].
- British guideline on the management of asthma. A national clinical guideline. British Thoracic Society and Scottish Intercollegiate guidelines network, 2016. Available: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/> [Accessed June 2019].

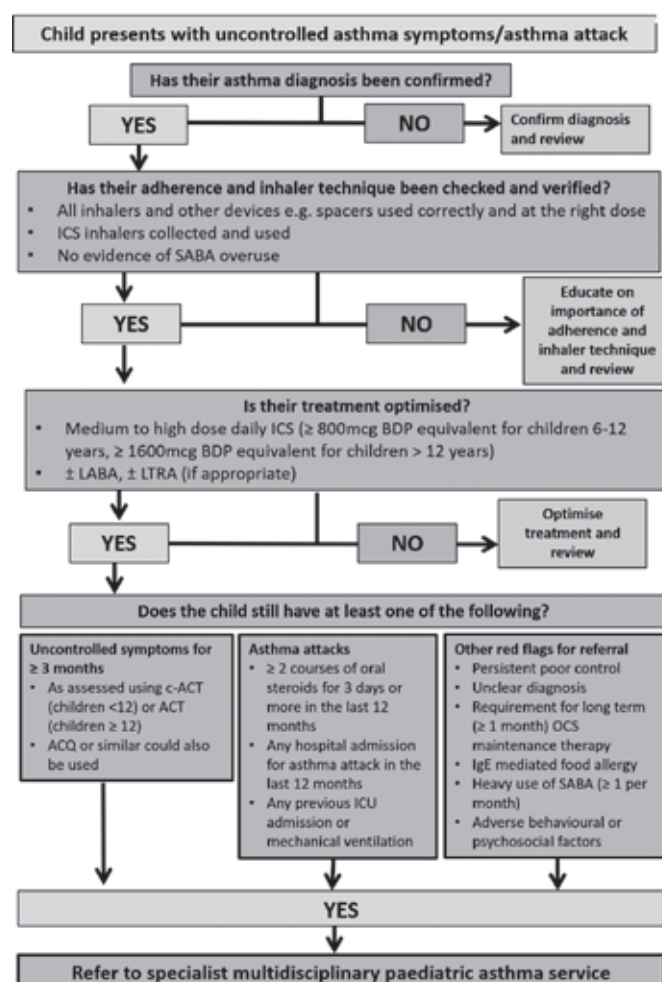


Figure 1 North West Midlands referral pathway for CYP with asthma. c-ACT, childhood asthma control test; ACQ, asthma control questionnaire; BDP, beclomethasone dipropionate; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting beta-2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting beta-2 agonist.

- Carroll WD, Wildhaber J, Brand PLP. Parent misperception of control in childhood/adolescent asthma: the room to breathe survey. *European Respiratory Journal* 2012;39:90–6.
- Wildhaber J, Carroll WD, Brand PLP. Global impact of asthma on children and adolescents' daily lives: the room to breathe survey. *Pediatr Pulmonol* 2012;47:346–57.
- Available: <https://www.judiciary.uk/wp-content/uploads/2016/01/Mills-2015-0416.pdf> [Accessed June 2019].
- Trivedi M, Denton E. Asthma in children and Adults—What are the differences and what can they tell us about asthma? *Front. Pediatr* 2019;7.
- Asthma UK. Difficult to control asthma, 2019. Available: <https://www.asthma.org.uk/advice/understanding-asthma/types/difficult-to-control-asthma/> [Accessed Aug 2019].
- Lang A, Carlsen KH, Haaland G, et al. Severe asthma in childhood: assessed in 10-year olds in a birth cohort study. *Allergy* 2008;63:1054–60.
- Ahmed H, Turner S. Severe asthma in children—a review of definitions, epidemiology, and treatment options in 2019. *Pediatr Pulmonol* 2019;54:778–87.
- Sheares BJ, Mellins RB, Dimaggio E, et al. Do patients of subspecialty physicians benefit from written asthma action plans? *Am J Respir Crit Care Med* 2015;191:1374–83.
- Asthma UK. Slipping through the net. The reality facing patients with difficult and severe asthma, 2018. Available: <https://www.asthma.org.uk/globalassets/getinvolved/external-affairs-campaigns/publications/severe-asthma-report/auk-severeasthma-gh-final.pdf> [Accessed June 2019].
- Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019;53:1901046.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
- Szefer SJ, Zeiger RS, Haselkorn T, et al. Economic burden of impairment in children with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2011;107:110–9.
- Novartis data on file.
- Asthma UK. Slipping through the net: the reality facing patients with difficult and severe asthma. Available: <https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk-severe-asthma-gh-final.pdf> [Accessed Jun 2019].
- Environmental audit Committee – written evidence (A299), 2010. Available: <https://publications.parliament.uk/pa/cm200910/cmselect/cmenvaud/229/229we26.htm#note56> [Accessed Jun 2019].
- Asthma UK. New treatments for severe asthma, 2019. Available: <https://www.asthma.org.uk/advice/severe-asthma/treating-severe-asthma/xolair-and-new-treatments/> [Accessed Jun 2019].
- Rabe KF, Adachi M, Lai CKW, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40–7.
- Gustafsson PM, Watson L, Davis KJ, et al. Poor asthma control in children: evidence from epidemiological surveys and implications for clinical practice. *Int J Clin Pract* 2006;60:321–34.
- Turner SW, Murray C, Thomas M, et al. Applying UK real-world primary care data to predict asthma attacks in 3776 well-characterised children: a retrospective cohort study. *NPJ Prim Care Respir Med* 2018;28.
- Hull SA, McKibben S, Homer K, et al. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. *NPJ Prim Care Respir Med* 2016;26.
- Suruki RY, Daugherty JB, Boudiaf N, et al. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med* 2017;17:74.
- Bracken M, Fleming L, Hall P, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child* 2009;94:780–4.
- van der Meer A-N, Pasma H, Kempenaer-Okkema W, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *Eur Respir J* 2016;48:726–33.
- NHS England. Specialised Respiratory Services (adult) – Severe Asthma, 2017. Available: <https://www.england.nhs.uk/publication/specialised-respiratory-services-adult-severe-asthma/> [Accessed Nov 2019].
- The bmj opinion. People with severe asthma are slipping through the net, 2018. Available: <https://blogs.bmj.com/bmj/2018/09/07/and-why-whom-people-with-severe-asthma-are-slipping-through-the-net/> [Accessed Nov 2019].
- Primary Care Commissioning. Designing and commissioning services for children and young people with asthma: a good practice guide, 2013. Available: <http://www.pcc-cic.org.uk/article/designing-and-commissioning-services-children-and-young-peopleasthma-good-practice-guide> [Accessed Nov 2019].

BMJ



Explore our BMJ podcasts
for exclusive extras

Get insights on the latest interviews, debates
and discussions in your specialty

For more information visit
podcasts.bmj.com

Orientação da *British Thoracic Society* para a utilização de macrólidos de longo prazo em adultos com doença respiratória

David Smith,¹ Ingrid Du Rand,² Charlotte Louise Addy,³ Timothy Collins,⁴ Simon Paul Hart,⁵ Philip J Mitchelmore,^{6,7} Najib M Rahman,⁸ Ravijyot Saggu⁹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-213929>).

¹North Bristol Lung Centre, Southmead Hospital, Bristol, UK

²Respiratory, Wye Valley NHS Trust, Hereford, UK

³Centre for Medical Education, Queens University Belfast, Regional Respiratory Centre, Belfast City Hospital, Belfast, UK

⁴Medical Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

⁵Cardiovascular and Respiratory Studies, Hull York Medical School/University of Hull, Hull, UK

⁶Institute of Biomedical and Clinical Science, College of Medicine & Health, University of Exeter, Exeter, UK

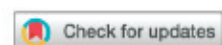
⁷Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, UK

⁸Oxford Respiratory Trials Unit and Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

⁹Pharmacy, University College London Hospitals NHS Foundation Trust, London, UK

Correspondência para

Dr David Smith, Southmead Hospital, North Bristol Lung Centre, Bristol BS10 5NB, UK; david.smith@nbt.nhs.uk



► <http://dx.doi.org/10.1136/thoraxjnl-2019-214039>



© Autor(es) (ou o(s) seu(s) empregador(es)) 2020. Não é permitida a utilização com fins comerciais. Consultar direitos e permissões. Publicado pela BMJ.

Para citar: Smith D, Du Rand I, Addy C, et al. Thorax 2020;75:370–404

SUMMARY OF RECOMMENDATIONS AND GOOD PRACTICE POINTS

Asthma

Recommendations

► Oral macrolide therapy could be considered to reduce exacerbation frequency in adults (50–70 years), with ongoing symptoms despite >80% adherence to high-dose inhaled steroids (>800 µg/day) and at least one exacerbation requiring oral steroids in the past year. This recommendation reflects the population within the AMAZES RCT which represents the highest quality evidence of macrolide therapy leading to a significant reduction in exacerbations. (Conditional)

► Treatment with azithromycin should be considered for a minimum of 6–12 months to assess evidence of efficacy in reducing exacerbations. (Conditional)

► Oral macrolide therapy should not be offered as a way to reduce oral steroid dose; in some individuals, this may result as a consequence of a reduction in exacerbations or symptoms. (Strong)

Good practice points

✓ Optimisation of other asthma therapies including establishing good adherence to inhaled therapies should be performed before considering a trial of oral macrolide therapy.

✓ Referral to a respiratory specialist or specialist asthma service should be considered prior to initiation of macrolide therapy aimed at reducing exacerbation frequency.

✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.

✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.

✓ Microbiological screening of sputum before and during macrolide therapy may be clinically helpful in patients who are able to expectorate sputum. This would allow monitoring for development of resistance and detect changes in microbial growth to direct appropriate antibiotic therapy if required. However, the resource implications of this approach have not been assessed.

✓ If oral macrolide therapy is considered, justification for ongoing treatment should be guided by clinical response based on specific outcome measures including exacerbation frequency, symptoms and quality of life assessed at baseline.

✓ A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg thrice weekly), a dose reduction to azithromycin 250 mg thrice weekly could be considered if macrolide therapy has been of clinical benefit.

✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.

✓ Symptom improvement with macrolide treatment may be minimal and not consistent across all people with asthma. If macrolide therapy is considered for symptom reduction, this should be for a defined period (6–12 months) and stopped if no symptomatic improvement is seen. Use of a validated symptom score, such as the ACQ, may be useful to help make this assessment less subjective.

✓ If the desired clinical outcome is achieved, the possibility of breaks in therapy may be considered to reduce treatment burden for patients. It is unclear whether this may also reduce antimicrobial resistance rates. Please see quick reference guide in online supplementary file 1.

Bronchiectasis

Recommendations

✓ Long-term macrolide treatment could be offered to reduce exacerbations in those with high exacerbation rates (ie, 3 or more per year). (Strong)

✓ The dosing regimens with the greatest supportive evidence, when using macrolides to reduce exacerbation rates, are azithromycin 500 mg three times a week, azithromycin 250 mg daily and erythromycin ethylsuccinate 400 mg twice a day. A starting dose of azithromycin 250 mg three times a week could be used to minimise side effect risk with subsequent titration according to clinical response. (Conditional)

► When using macrolides to reduce exacerbation rates, therapy should be offered for a minimum of 6 months. (Strong)

► Macrolides can be considered with the aim of improving quality of life but may require a long period of therapy (eg, 1 year) for significant effects. (Conditional)

Good practice points

✓ Therapies should be optimised in accordance with BTS Bronchiectasis Guidelines before considering long-term macrolide therapy (eg, airway clearance techniques and attendance at pulmonary rehabilitation courses).

✓ Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.

✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.

✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance. Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. When evaluating for NTM infection, macrolides should not be used for 2 weeks before microbiological testing.

✓ Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for bronchiectasis.

✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.

✓ Subsequent follow-up at 6 months and 12 months should determine whether benefit is being derived from therapy. If there is no benefit, treatment should be stopped.

✓ Even if benefit is seen, consideration should be given to stopping treatment for a period each year, for example, over the summer. Such a drug holiday may help with reducing the development of resistance while maintaining efficacy because the vicious cycle has been broken. See quick reference guide in online supplementary file 1.

Chronic obstructive pulmonary disease

Recommendations

► Long-term macrolide therapy could be considered for patients with COPD with more than three acute exacerbations requiring steroid therapy and at least one exacerbation requiring hospital admission per year to reduce exacerbation rate. (Conditional)

► Long-term macrolide therapy could be considered for a minimum of 6 months and up to 12 months to assess the impact on exacerbation rate. (Conditional)

Good practice points

✓ Non-pharmacological and pharmacological therapies should be optimised prior to considering long-term macrolide therapy. This includes smoking cessation, optimised inhaler technique, optimised self-management care plan, airway clearance techniques and attendance at pulmonary rehabilitation courses.

✓ Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.

✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.

✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.

✓ Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. Repeat assessments are recommended with clinical decline or during exacerbations to monitor resistance patterns.

✓ Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for patients with COPD and a CT scan should be considered to exclude a possible diagnosis of bronchiectasis.

✓ A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg thrice weekly), a dose reduction to azithromycin 250 mg thrice weekly could be considered if macrolide therapy has been of clinical benefit.

✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.

✓ Subsequent follow-up at 6 and 12 months should determine whether benefit is being derived from therapy by using objective measures such as the exacerbation rate, CAT score or Quality of Life as measured by a validated assessment tool such as SGRQ. If there is no benefit treatment should be stopped.

✓ It is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD unless another antibiotic with potential to affect the QT interval has also been prescribed. See quick reference guide in online supplementary appendix 1.

Bronchiolitis obliterans (including post transplantation)

Recommendations

► Low-dose, long-term azithromycin (250 mg thrice weekly) could be considered to prevent the occurrence of BOS post lung transplantation. (Conditional).

► Low-dose azithromycin (250 mg alternate days for a trial period of 3 months) could be considered to treat BOS occurring in lung transplant recipients. (Conditional) use of macrolides in other respiratory conditions.

Cough

Recommendations

► Long-term macrolide antibiotics should not be used to manage patients with unexplained chronic cough. (Conditional)

Organising pneumonia

There is insufficient evidence to make a recommendation.

Safety issues

Gastrointestinal effects

Good practice points

✓ Prior to initiating low-dose macrolide therapy, patients should be warned of the possibility of gastrointestinal side effects.

✓ Gastrointestinal side effects may be ameliorated by dose reduction although this may also reduce clinical efficacy.

✓ Clinicians should carefully consider the risk-to-benefit balance when considering therapy for those with pre-existing gastrointestinal symptomatology.

Cardiac effects

Good practice points

✓ Prior to initiating low-dose macrolide therapy, patients should be asked if they have a history of heart disease, previous low serum potassium measurements, a slow pulse rate, a family history of sudden death or known prolonged QT interval. Patients with such a history should not receive low-dose macrolide therapy without careful consideration and counselling of the increased risk of adverse cardiac effects.

✓ Prior to initiating low-dose macrolide therapy, a drug history looking for agents that might prolong the QTc interval should be sought (see online supplementary appendices 3 and 4). Patients taking such agents should not receive low-dose macrolide therapy.

✓ Prior to initiating low-dose macrolide therapy, an ECG should be performed to exclude a prolonged QTc interval defined as >450 ms for men and >470 ms for women (see methodology in online supplementary appendices 3 and 4). Patients with a prolonged QTc interval should not receive low-dose macrolides.

✓ One month after initiating low-dose macrolide therapy, a second ECG should be performed to exclude the development of a prolonged QTc interval. Patients who develop a prolonged QTc interval on low-dose macrolides should stop the macrolide.

✓ If any new drug that could potentially prolong QTc time is started or if dose increases are made, repeat ECG assessment.

Ototoxicity

Good practice point

✓ Prior to initiating low-dose macrolide therapy, patients should be asked if they have a history of hearing or balance difficulties. Such patients should be made aware of the potential for a further, almost always reversible, deterioration good practice points in hearing or balance with macrolide therapy. Patients with pre-existing hearing or balance difficulties who wish to proceed with treatment should be asked to report any change in hearing or balance promptly.

Other side effects

Good practice points

✓ Prior to initiating low-dose macrolide therapy, baseline liver function tests (LFTs) should be checked.

✓ LFTs should be checked after 1 month of treatment and then every 6 months thereafter for the duration of therapy. antimicrobial resistance.

Good practice points

- ✓ The risks associated with increasing antimicrobial resistance should be discussed with patients prior to starting low-dose macrolide therapy. Patients should understand the risk that there may not be an effective antibiotic for them, or someone else, when needed in the future.
- ✓ Prior to initiating low-dose macrolide monotherapy, patients should be asked if they have a history of previous or current NTM infection or disease. Current NTM infection should be managed with reference to BTS guidance and precludes low-dose macrolide monotherapy. Successfully treated NTM disease should not preclude low-dose macrolide monotherapy.
- ✓ If there is any clinical suspicion of possible NTM disease, patients should be screened via examination of sputum samples prior to starting therapy. If positive for recognised potential pathogenic species, low-dose macrolide prophylaxis is contraindicated.

SECTION 1: INTRODUCTION

Aim of the guideline

The aim of this guideline is to examine the evidence for the use of long-term, low-dose macrolide agents in the therapy of adult respiratory diseases and to develop guidance for clinicians in such use of these agents.

Intended users of the guideline and target patient populations

These guidelines will be of interest to UK-based clinicians caring for adults with respiratory disease including respiratory physicians, acute/general medicine physicians and respiratory specialist nurses. The guidelines may also be of interest to GPs, community matrons and practice nurses, hospice staff and community respiratory teams, physiotherapists, microbiologists, pathologists, pharmacists, haematologists and lung transplant teams.

Scope of the guideline

The Guideline Development Group (GDG) has examined the use of macrolides in adults (>16 years) where the duration of treatment exceeds that usually employed to treat an acute infection and the dosage is less than that usually employed to treat an acute infection. Such usage is considered to be exerting an effect through mechanisms other than a direct antibacterial one, commonly described as immunomodulatory mechanisms. We have characterised this as long-term, low-dose usage and have examined such usage (often in comparison with conventional therapy) in the following conditions:

- Asthma.
- Bronchiectasis.
- COPD.
- Bronchiolitis obliterans.
- Chronic cough.
- Organising pneumonia.
- Diffuse panbronchiolitis.

In addition, the GDG has looked at safety issues surrounding the long-term use of macrolides at both patient and population levels to help formulate pragmatic guidance in this area based on the best available evidence combined with clinical experience. Areas not covered by the guideline These guidelines exclude paediatric practice. The use of macrolides in cystic fibrosis has not been included recognising the parallel work of the National Institute for Health and Care Excellence (NICE) (Cystic fibrosis: long term azithromycin. Evidence Summary ESUOM.³⁷ November 2014) in this area. Long-term macrolides for chronic rhinosinusitis have not been included. The use of macrolides as antibacterial agents to treat respiratory infection is excluded.

Limitations of the guideline

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations cited here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each

Table 1 Summary of outcome measures

Population	Intervention	Control	Outcomes
Adults with asthma	Long-term, low-dose macrolides	Placebo	▶ Quality-of-life measures ▶ Symptom improvement/symptom score ▶ Exacerbation rates ▶ Hospital admission rate ▶ Disease progression and changes in lung function tests ▶ Mortality ▶ Exercise capacity/tolerance ▶ Sputum volume/colour/character and microbiological resistance/dysbiosis ▶ Drug monitoring/side effects/toxicity
Adults with bronchiectasis			
Adults with COPD			
Adults with bronchiolitis obliterans			
Adults with chronic cough			
Adults with organising pneumonia			
Adults with diffuse panbronchiolitis			

patient, in consultation with the patient and/or their guardian or carer. The GDG recognises that none of the macrolide antibiotics are licensed in the UK for long-term low-dose usage as immunomodulatory agents at the time of guideline development. members of the GdG

The GDG was chaired by two respiratory consultants—Dr David Smith (DS) and Dr Ingrid Du Rand (IDR). The GDG had a wide membership and included colleagues from respiratory medicine, pharmacy and microbiology. A patient representative was on the group for the duration of the process. Those on the group were not required to be BTS members. Mrs Joan McCarthy was the lay representative. A full list of members can be seen at online supplementary appendix 2.

Acknowledgements

The GDG is grateful to the Standards of Care Committee for assistance during the development of the guideline, and particular thanks are due to Dr Toby Capstick and Dr Mike Crooks for their input and advice in relation to certain sections of the guideline.

SECTION 2: METHODOLOGY OF GUIDELINE PRODUCTION

Establishment of guideline development group

The GDG was convened in June 2016, with the first meeting taking place in October 2016. The full GDG met three times during the development of the guideline and kept in close contact by teleconference/WebEx and email throughout the process.

Methodology

This is the first BTS guideline to use the GRADE approach as part of the process of guideline development. Previous guidelines have used the SIGN methodology. BTS has made this change reflecting common practice in guideline development internationally across all medical specialities. The advantages of the GRADE approach are described in detail in the GRADE handbook and the BTS GRADE guideline production manual. GRADE specifies an approach to framing questions, choosing outcomes of interest and rating their importance, evaluating the evidence, and incorporating evidence with considerations of values and preferences of patients and society to arrive at recommendations.¹ The methodology used to write the guideline adheres strictly to the criteria as set by the AGREE II collaboration, which is available online (www.agreetrust.org/resource-centre/agree-ii/). The British Thoracic Society Standards of Care Committee guideline production manual is available online (<https://www.brit-thoracic.org.uk/quality-improvement/guidelines/>).

Summary of key questions, outcomes and literature search

Clinical questions were formulated in the PICO (Patient, Intervention, Comparison and Outcome) format (see table 1). The key questions are summarised below.

1. Should long-term, low-dose macrolides be used in the treatment of adults with asthma?
2. Should long-term, low-dose macrolides be used in the treatment of adults with bronchiectasis?
3. Should long-term, low-dose macrolides be used in the treatment of adults with chronic obstructive pulmonary disease?
4. Should long-term, low-dose macrolides be used in the treatment of adults with bronchiolitis obliterans?

5. Should long-term, low-dose macrolides be used in the treatment of adults with chronic cough?
6. Should long-term, low-dose macrolides be used in the treatment of adults with organising pneumonia?
7. Should long-term, low-dose macrolides be used in the treatment of adults with diffuse panbronchiolitis?

The following patient-centred outcomes were identified by the group when the scope of the guideline was agreed:

Quality-of-life measures.

Symptom improvement/symptom score.

Exacerbation rates.

Hospital admission rate.

Disease progression and changes in lung function tests.

Mortality.

Exercise capacity/tolerance.

Sputum volume/colour/character and microbiological resistance/dysbiosis.

Drug monitoring/side effects/toxicity.

The PICO framework was used to define the scope of the guideline and formed the basis of the literature search. The initial search was completed in February 2017 by York University. Systematic electronic database searches were conducted in order to identify all papers which might potentially be included in the guideline. For each question, the following databases were searched: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE In-Process, EMBASE and PubMed. The search strategy is available for review in online supplementary appendix 1.

Appraisal of the literature

The literature search was run in 2016. The search was limited to papers published in English. The search identified a total of 5225 abstracts; after initial screening, this was reduced to 1152. Criteria formulated for initial screening of the abstracts were

- Whether the study addressed the clinical question
- Whether the appropriate study type was used to produce the best evidence to answer the clinical question.
- Abstract was in English.
- Studies in which macrolide therapy was used to treat acute respiratory tract infection were rejected.
- Abstracts were not rejected on the basis of the journal of publication, or the country in which the research was performed.

The full list of abstracts was retained and is kept in an archive. The literature search was repeated in December 2017 to capture additional published evidence while the guideline was in development prior to finalising the draft document. Additional references were included from critical appraisal of the literature and review of existing evidence base as appropriate.

Letters, conference papers and news articles were then removed—518 abstracts were rejected at this stage. IDR and DS read the remaining abstracts, marked those considered relevant to the scope of the guideline and allocated each relevant abstract to a clinical question(s). In total, 634 abstracts were allocated to clinical question(s).

The literature search was updated in late 2017 and identified 138 additional abstracts that were reviewed and 14 papers were selected to be critically appraised. GDG members were allocated to work on individual questions in small groups.

Each abstract was read and at least two members agreed whether the paper was relevant, possibly relevant or irrelevant to the particular clinical question. Papers were excluded at the title/abstract sift if the following applied:

- If the paper did not address the clinical question and at least one of the outcomes concerned.
 - If it was a case series of less than 20 patients—however, this was not an absolute cut-off. Professional judgement was applied such that some smaller case series were considered if evidence was sparse, and indeed some case reports of more than 20 patients were excluded if there was higher quality evidence available.
 - If the language of the full paper was not English.
- Full papers were obtained for all relevant, or possibly relevant, abstracts. Each paper was read in full and critically appraised by at least two members of the GDG to confirm relevance to the clinical question and the presence of at least one outcome of interest.

Table 2 Categories of evidence

	Characteristics	Confidence
High	Based on consistent results from well-performed randomised controlled trials	Further research is very unlikely to change the estimate of the effect
Moderate	Based on randomised controlled trials where there is evidence of bias or from other well-conducted study types (eg, well-executed observational studies)	Further research is likely to have an impact on the estimate of the effect
Low	Based on observational evidence or from controlled trials with several serious limitations	Further research is likely to have an important impact
Very low	Based on case studies or expert opinion	Estimates of effect are far from certain and more research is needed

Each paper was then appraised by outcome(s), to generate a best estimate of the effect on each outcome and an index of the uncertainty associated with that estimate where possible. An evidence profile entry was completed for each outcome which included grading of the quality of the evidence. The type of evidence available for each outcome varied from systematic reviews through to case series; for each outcome, the highest quality evidence available was included. GRADEPro was used to generate the evidence profiles, published online on the BTS website where they are available for review (see online supplementary appendix 2). GRADEPro (<https://gradepro.org/>) is an easy-to-use, all-in-one web-based electronic guideline development tool to support guideline development using the GRADE process and methodology. In addition, it provides an electronic platform to present evidence tables, considered judgement and assessment of the evidence base.

The GRADE approach to rating the quality of evidence begins with the study design (table 2) and then, through a process of considered judgement, applies five reasons to possibly rate down the quality of evidence and three reasons to possibly rate up the quality (table 3).

The GDG reviewed each clinical question during the regular meetings and consensus was reached. In assessing the evidence the guideline development group combined low and very low evidence into one category (Low) as the body of evidence was limited. development of recommendations

Having generated evidence profiles for each of the clinical questions the GDG as a whole then considered the importance of each of the outcomes for each clinical question and proceeded to grade the overall body of evidence for critical and important outcomes.

The GDG went on to decide on the direction and strength of recommendations considering the quality of the evidence, the balance of desirable and undesirable outcomes and the values and preferences of patients and others. GRADE specifies two categories of strength of a recommendation as shown in table 4. Good practice points (GPPs) were developed by consensus in areas where there was no quality evidence but the GDG felt that some guidance based on the clinical experience of the GDG might be helpful to the reader. These are indicated as shown below.

√ Recommended best practice based on the clinical experience of the guideline development group

From the outset, it was acknowledged that there would be little high-quality evidence for some of the clinical questions identified. In this instance, low-grade evidence was considered, along with expert opinion via consensus at the meetings. Cost-effectiveness was not considered in detail as in-depth economic analysis of recommendations falls outside of the scope of the BTS guideline production process.

Table 3 Categories of evidence

	Confidence
Decrease grade if*	Serious or very serious limitation to study quality. Important inconsistencies in results Some or major uncertainty about directness of the evidence Imprecise or sparse data (relatively few participants and/or events). High probability of reporting bias.
Increase grade if	Magnitude of the treatment effect is very large and consistent. Evidence of a large dose-response relation. All plausible confounders/biases would have decreased the magnitude of an apparent treatment effect.

*Each quality criterion can reduce the quality by one or, if very serious, by two levels. See BTS GRADE guideline production manual for further details (<https://www.brit-thoracic.org.uk/quality-improvement/guidelines/>).

Table 4 Explanation of the terminology used in BTS recommendations

Strength	Benefits and risks	Implications
Strong. It is recommended and so 'offer'	Benefits appear to outweigh the risks (or vice versa) for the majority of the target group	Most service users would want to or should receive this intervention
Moderate	Risks and benefits are more closely balanced, or there is more uncertainty in likely service users values and preferences	The service users should be supported to arrive at a decision based on their values and preferences

However, the GDG were asked to be mindful of any potential economic barriers to the implementation of recommendations and GPPs. Research recommendations were also highlighted and are listed in PICO format in an online supplementary appendix 3.

Drafting the guideline

The GDG corresponded regularly by email and meetings of the full group were also held in the period between July 2016 and early 2019. The guideline was discussed at an open session at the BTS Winter Meeting in December 2018. A revised draft guideline document was circulated to all the relevant stakeholders for consultation in December 2018 followed by a period of online consultation. The BTS SOCC reviewed the draft guideline in March 2018 and March 2019.

Review of the guideline

This guideline topic was chosen to inform practice in a growing clinical area, but also to act as a pilot for the use of GRADE methodology for all future BTS guidelines. The GDG recognise that the topic area would include a range of diseases with differing levels of evidence and thus act as a useful learning exercise for the introduction of GRADE methodology. It is not proposed to update this guideline as a distinct entity—the intention is for macrolide use to be encompassed in future diseasespecific guideline updates. declarations of interests BTS Declarations of Interest forms have been completed by all members for each year they were part of the GDG. Details of these forms can be obtained from BTS Head Office. "Declarations of Interests" was a standing item at each GDG meeting.

Stakeholders

Stakeholders were identified at the start of the process. All stakeholder organisations were notified when the guideline was available for public consultation and a list is published in online supplementary appendix 2.

Other available guidance

The GDG were aware of parallel workstreams within the BTS (eg, the BTS guideline for bronchiectasis in adults)² and in other organisations (eg, NICE) either complete or in progress at the time this guideline began development. Some of those in progress have subsequently been published and overlap with this guideline. The majority of these guidelines are disease specific rather than focusing on a single drug group. The pool of evidence available for these guidelines is the same, but the sample drawn from that pool is often slightly different. In addition, the methodology applied and the resources available to individual organisations are also variable. It is thus not surprising that the recommendations sometimes differ between contemporaneous documents. We have included a list of recently published guidelines and Cochrane reviews which overlap with this document.

BTS Guideline for Bronchiectasis in Adults 2019²

NICE CF diagnosis and management Oct 2017³

NICE Asthma diagnosis, monitoring and management Nov 2017⁴

NICE Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing Dec 2018⁵

NICE Bronchiectasis (acute exacerbation): antimicrobial prescribing Dec 2018⁶

NICE COPD guideline 2018⁷

GOLD guideline COPD 2019⁸

ERS/ATS COPD Exacerbations 2017⁹

Cochrane Prophylactic antibiotic therapy for COPD 2018¹⁰

Cochrane Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults 2017¹¹

Cochrane Antibiotics for exacerbations of asthma 2018¹²

Cochrane Macrolide antibiotics for bronchiectasis 2018¹³

Cochrane Macrolides for chronic asthma 2015¹⁴

GINA 2018 Global Strategy for Asthma Management and Prevention¹⁵
Cochrane Adverse events in people taking macrolide antibiotics vs placebo for any indication 2019¹⁶ Within each of sections 4, 5 and 6, a summary of other guideline recommendations for that disease has been included.

SECTION 3: INTRODUCTION TO THE USE OF MACROLIDES IN RESPIRATORY CARE

The term macrolide describes compounds with a macrocyclic lactone ring of 12 or more elements. Within this definition are a variety of drugs including antibiotics, antifungals, prokinetic agents and immunosuppressants. The most commonly used macrolide antibiotics have 14-membered or 15-membered lactone rings and include the first macrolide, erythromycin, which was launched commercially in 1952. Further 14-membered macrolides include clarithromycin and roxithromycin; the 15-membered azithromycin became available in the 1980s. Macrolide antibiotics are active orally, have excellent tissue penetration and antimicrobial activity against many Grampositive bacteria, some Gram-negative organisms and some 'atypical' respiratory pathogens such as legionella and mycoplasma together with some mycobacterial species. This makes them a popular choice for respiratory tract infections.

Early studies with macrolide antibiotics in asthma in short antimicrobial courses¹⁷ and in longer, lower-dose regimens¹⁸ were the first to suggest a possible non-antimicrobial mode of action, possibly as a steroid-sparing agent. Diffuse panbronchiolitis (DPB) was recognised as a distinct clinical entity in Japan in 1969¹⁹ having a poor prognosis, 25% mortality at 10 years without *Pseudomonas aeruginosa* infection or >75% with *P. aeruginosa*. The first report of a dramatic response to low-dose, long-term treatment with erythromycin appeared in 1987²⁰ and led to further confirmatory studies of macrolide efficacy in DPB. This acted as a catalyst for the subsequent exploration of the non-antimicrobial effects of macrolides.²¹

The mechanisms behind the immunomodulatory effects of macrolides have been widely researched. They include alterations in airway secretions through effect on ion transport and mucus production. Changes in the inflammatory process occur through effects on cytokine production, adhesion molecule expression and the functions of inflammatory cells, airway epithelial cells and other cells. Sublethal effects on bacteria include disruption of biofilms, interference with quorum sensing and reduced bacterial adherence, toxin production and mobility.²² The recognition of these immunomodulatory properties has led to the investigation of potential benefit from low-dose, longterm macrolides in a number of other chronic inflammatory airway diseases including cystic fibrosis, bronchiectasis, COPD, asthma, cryptogenic organising pneumonia (COP), chronic rhinosinusitis and bronchiolitis obliterans. In some of these conditions (eg, cystic fibrosis), the evidence base supporting the use of macrolides is large but in others (eg, COP) it is small.

Alongside this increase in the longer-term use of macrolides as immunomodulatory agents, concerns regarding the safety of these drugs used in this way have appeared.²³ Gastrointestinal side effects are unsurprisingly common but rarely serious; however, ototoxicity and effects on myocardial tissue are potentially more harmful. Alterations in the microbiome of individuals and populations and the rapid emergence and persistence of macrolide-resistant organisms have also prompted discussion.²⁴ It should also be noted that the rising rates of antimicrobial-resistant pathogens is of global concern. Any consideration of the benefits of an individual patient receiving an antibiotic needs to be carefully balanced against the risk of increased resistance—both for that individual patient but also for other individuals, both now and in the future.

It was against this background of expanding use of macrolides in inflammatory respiratory diseases that BTS decided to commission a guideline aimed at supporting best practice in a developing arena.

SECTION 4: ASTHMA

Introduction

The majority of asthma treatments aim to reduce airway inflammation with subsequent symptomatic improvement. Pathologically, asthma is characterised by airway inflammation and bronchial hyper-responsiveness. Airway inflammation can be predominantly neutrophilic or eosinophilic in nature.¹⁵ Despite an increase in therapeutic options and clear guidance on stepwise management, asthma symptoms can be difficult to manage and exacerbations remain a predominant feature for many. Adherence to treatment can be challenging. Newer therapeutic options, including biologics, can be expensive, require frequent monitoring and are limited to specific clinical phenotypes.^{15 25}

There has been significant interest in the potential role of oral macrolide therapy as an option in asthma. It is relatively inexpensive, easy to adhere to and has a physiologically relevant mechanism of action which may reduce airway inflammation in asthma. There is also evidence suggesting increasing asthma severity may be linked to chronic colonisation with *Chlamydiae* and *Mycoplasma pneumoniae*. It has therefore been postulated that benefit from macrolide therapy may also be through its antibacterial effects on these and other lung organisms.²⁶

As a consequence, there have been a number of studies over several decades examining the response to macrolide therapy in asthma which vary considerably in design and outcome measures. The first study examining the role of macrolides in asthma was their use as a steroid-sparing agent in 1970.¹⁷ Studies since have examined their role in reducing airway inflammation and bronchial hyper-responsiveness, impact on symptoms and quality of life and most recently on their ability to reduce exacerbation frequency.

Evidence base

Examining the evidence base for macrolide therapy in asthma is particularly challenging because of the significant heterogeneity in study designs, outcome measures and study populations, as well as the heterogeneity of the asthma population itself. A Cochrane review of macrolide therapy in asthma identified significant publication bias, poor study design and lack of consistency in outcome measures as the key barriers to making recommendations based on the available evidence.¹⁴ Considering the size of the clinical population and burden of disease in this population,¹⁵ there is a relative paucity of high-quality evidence regarding macrolide use in asthma. There are relatively few studies with small study populations which are often underpowered to detect appropriate changes in the outcome measures used. The study populations are also varied limiting the applicability of their results to the wider asthma population and the ability to determine where macrolide therapy should sit within an asthma treatment regime. Despite this, across multiple outcome measures statistical significance was achieved in many studies, but the magnitude of the changes seen were very small. The clinical significance of these changes varies from unknown to unlikely to be of any clinical benefit. This is reflected in the recommendations made in this guideline. No evidence of the impact of macrolide therapy on mortality, exercise capacity, disease progression or sputum production in people with asthma was found therefore no recommendations in regard to these outcomes can be made in this guideline. In all cases, macrolides should be considered after current therapy has been optimised and adherence established.

Other recent guidance

Recommendations on macrolide therapy are not included in current NICE/BTS/SIGN asthma guidelines.^{4 25} NICE guidance suggests referral to an asthma specialist and consideration of the addition of a trial of 'an additional drug' (which could include a macrolide) if asthma is uncontrolled in adults (aged 17 and over) on a moderate maintenance ICS dose with a LABA (either as MART or a fixed-dose regimen).

Quality of life (QoL)

QOL was the most consistently assessed outcome measure in studies of macrolide therapy in asthma. All but one study²⁷ used the well-validated Asthma Quality of Life Questionnaire (AQLQ) score. This score was first validated in 1992 and has a minimal important difference (MID) of 0.5.²⁸ This is critical to appraising this body of evidence, as in similarity with the symptomatic improvements seen, after treatment with macrolides there is consistent small but statis-

tically insignificant ($p > 0.05$) improvement in QOL seen across the majority of studies.^{14 27 29–36} In two studies comparing macrolide therapy with placebo,^{33 34} this change reached the MID of the AQLQ. The first used 8 weeks' treatment with clarithromycin³⁴ and the second was the open-label treatment arm of a study of 48 weeks' treatment with azithromycin.³³

It is therefore clear that treatment with macrolides may result in measurable improvements in QOL for people with asthma, but the clinical impact of these changes remains unknown and may be very small.

Symptoms

Thirteen studies used symptom scoring as an outcome in response to macrolide therapy.^{14 27 29–31 34–41} There was considerable variation in the scoring systems used, from the validated Asthma Control score (ACQ) to simplified unvalidated scoring systems, created specifically for an individual study. Overall,¹⁰ of the studies demonstrated a reduction in symptoms. Three studies^{29 31 33} demonstrated an increase in symptoms, of which only one used a validated and reproducible symptom score. Although the majority of studies demonstrated an improvement, the actual changes were minimal, unlikely to be of clinical significance and reached statistical significance in only three cases.^{37 38 41} None of the studies using the ACQ score demonstrated a change which would meet the ACQ minimal important difference (MID) (0.5).⁴²

Further work is needed to see if these improvements may be of greater significance over more prolonged treatment periods, and whether symptomatic improvement is related to the impact of macrolide therapy on exacerbation rate.

Exacerbations

Exacerbations of asthma are defined as an increase in symptoms, accompanied by a reduction in peak flow rate (PEFR), of graded severity dependent on the degree of clinical and PEFR deterioration.^{4 25} Exacerbation rate is the definitive outcome measure in regard to the clinical efficacy of macrolides in other respiratory diseases, and the major purported driver for their use in cystic fibrosis, bronchiectasis and COPD.¹⁴ Two studies^{30 40} have been specifically designed to address this question in asthma. In other studies, exacerbations have been measured as a secondary outcome, with differing definitions between studies and insufficient statistical power to detect a reduction in exacerbation frequency. A meta-analysis of these studies showed exacerbations requiring steroids in 19.6% (31/158) of those treated with macrolides and 24.2% (32/132) of those not receiving macrolide treatment.¹⁴ However, this reduction was not sufficient to reach statistical significance ($p > 0.05$).

Of the two studies^{30 40} specifically designed to determine a reduction in exacerbation frequency in response to azithromycin, the AMAZES trial demonstrated a significant reduction in exacerbations ($p < 0.0001$),⁴⁰ but the AZISAST trial did not ($p = 0.68$).³⁰ This may reflect the duration of treatment (AMAZES=48 weeks; AZISAST=6 months), dose effect (AMAZES=500 mg thrice weekly; AZISAST=250 mg thrice weekly) or differing study populations. AMAZES recruited a larger population ($n=420$) on high-dose inhaled steroids with an average of one exacerbation in the previous year, whereas the AZISAST population was smaller ($n=109$) with higher inhaled steroid doses and two exacerbations in the previous year (see table 5). Both studies also had slightly differing definitions of an exacerbation. These studies are the highest quality evidence found for the purposes of this guideline and were suitably powered to detect a change in exacerbation frequency.

The AZISAST study demonstrated no significant difference between exacerbation rates with 48% (26/54) of the placebo group and 47% (26/55) of the azithromycin group experiencing an exacerbation (relative risk 0.98, 95% CI 0.68 to 1.43, $p = 0.68$).³⁰ In AMAZES, 61% (127/203) of the placebo group experienced an exacerbation compared with 44% (94/213) of the azithromycin group giving an incidence rate ratio of 0.59 (95% CI 0.47 to 0.74, $p < 0.0001$)⁴⁰ (see table 5). Both studies assessed whether the predominant type of lung inflammation impacted the effectiveness of macrolide therapy.

In a predefined subgroup analysis of the AZISAST population, those with non-eosinophilic asthma showed a significant reduction in exacerbations in response to azithromycin treatment, with exacerbations occurring in 33% (9/27) of the azithromycin group compared with 62% (18/29) of the placebo group (relative risk 0.54, 95% CI 0.29

to 0.98, $p=0.037$).³⁰ In AMAZES, both those with eosinophilic asthma and non-eosinophilic asthma demonstrated a reduction in exacerbations, with a slightly greater reduction seen in the eosinophilic group. The incidence rate ratio in the eosinophilic group was 0.52 (95% CI 0.29 to 0.94, $p=0.030$) and 0.66 (95% CI 0.47 to 0.93, $p=0.019$) in the non-eosinophilic group.⁴⁰ This difference in outcomes may be partly explained by the differing definition of phenotypes between the two studies. In AZISAST, non-eosinophilic asthma was defined by a fraction of exhaled nitric oxide (FeNO) lower than the upper limit of normal and a blood eosinophilia $\leq 200/\mu\text{L}$.³⁰ In AMAZES, non-eosinophilic asthma was defined by a baseline sputum eosinophil count $<3\%$ or blood eosinophil count $<300/\mu\text{L}$ if sputum unavailable.⁴⁰

Overall, this evidence suggests that macrolide therapy may vary in its effectiveness between differing asthma phenotypes and that clinical benefit may be determined by more than the predominant type of inflammation. Further work is needed to investigate the impact of macrolides on exacerbation rate in differing asthma phenotypes and populations. However, it appears from AMAZES⁴⁰ that there is evidence of a reduction in exacerbations, but studies may need to run in larger populations for a longer duration to assess this effect successfully.

Steroid dose reduction

The original studies of macrolide use in asthma had the aim of reducing steroid dosage,¹⁷ but this has not been the stated outcome of a study using macrolide therapy since the 1990s. With the advent of newer biologic therapies and the focus on clinical phenotyping, there has been a move away from using therapies as steroid-sparing agents, towards a stratified approach to asthma therapy.

The three studies using steroid reduction as an outcome all used troleandomycin for between 2 and 52 weeks.^{43–45} All showed a reduction in steroid dosage, which has been confirmed in two Cochrane Reviews.^{14,39} However, these studies also included paediatric populations. Troleandomycin is also not widely used and is not available in the UK.

Lung function/pefr

FEV₁ remains a key outcome measure in trials of airways diseases. However, in asthma, FEV₁ can show considerable variation and is used as a secondary outcome measure in many studies. Peak flow was used frequently as a primary and secondary outcome, but with considerable variation in timing, rigour of performance and units of measurement. Overall FEV₁ improved in response to oral macrolide therapy, but to a small degree which may not result in any clinical improvement.^{14,31,35,37,39,46} This is illustrated by the results of four meta-analyses which individually compared FEV₁ responses across 15 studies using a range of macrolides. The Cochrane meta-analysis demonstrated a 0.08 L (95% CI 0.02 to 0.14 ($p=0.0097$)) improvement in FEV₁ (47); the Tong et al meta-analysis showed a 0.11 L (95% CI 0.06 to 0.16 ($p<0.001$)) improvement³⁶; and Reiter et al showed no effect on FEV₁ (standardised mean difference (SMD) 0.05 (95% CI -0.14 to 0.25 ($p=0.60$)).⁴¹ FEV₁ (% predicted) was only analysed in the Tong et al meta-analysis, showing a SMD of 0.27% (95% CI 0.05 to 0.59 ($p=0.10$)).³⁶ The fourth meta-analysis was confined to studies examining troleandomycin, showing a 0.06 L (95% CI -0.8 to 0.92 ($p=0.88$)) change in FEV₁.³⁹

Morning PEF was the most commonly measured parameter across studies. A positive change in morning PEF was seen in several studies, of a relatively smaller magnitude than that seen in FEV₁.^{14,30,35,36,41}

The Cochrane and Tong et al meta-analyses showed a 2.22 L/min (95% CI 9.73 to 14.17 ($p=0.72$))¹⁴ improvement and a SMD 0.25 (95% CI 0.1 to 0.39 ($p=0.001$))³⁶ in morning PEF, respectively. A third meta-analysis by Reiter et al also showed a 6.7 L/min (95% CI 1.35, 12.06 ($p=0.014$)) improvement, but this analysis included paediatric study populations.⁴¹ The change in evening PEF is more mixed across studies, with some showing a reduction³⁵ rather than improvement, although with a smaller evidence base.^{14,29,30} With the known variability of PEF in asthma, again it is difficult to judge the clinical importance of these changes.

Inflammation

Studies examining the impact of oral macrolide therapy on inflammation in asthma have used a variety of outcome measures in both blood and sputum. In keeping with common clinical phenotypes, the impact of macrolides on both neutrophilic and eosinophilic inflammation has been assessed. Two meta-analyses¹⁴ examined the effect of macrolide therapy on sputum and blood eosinophil counts measured in three separate RCTs after treatment with roxithromycin, clarithromycin and azithromycin. Consistent reductions in blood eosinophils were shown (mean difference (MD) -33.5 (95% CI -30.9 to -36.11) $\times 10^4/\text{mL}$ ($p<0.00001$)), but only the study examining clarithromycin (MD $-74\times 10^4/\text{mL}$) demonstrated a reduction in sputum eosinophils.³⁷

Five studies examined the impact of roxithromycin,⁴⁶ clarithromycin³⁷ and azithromycin³¹ on sputum neutrophils. One study demonstrated an increase in sputum neutrophils (MD 19.2 (95% CI -24.2 to 62.6), $p>0.05$) in response to azithromycin,⁴⁷ but pooled results of the other studies, as part of a meta-analysis, demonstrated an overall reduction of -0.25% (95% CI -0.62 to 0.13 , $p=0.20$).³⁶

Emerging biomarkers in the form of matrix metalloproteinase (MMP-9), neutrophil elastase and eosinophilic cationic protein (ECP) have also been examined. Clarithromycin resulted in a reduction in sputum MMP-9 and neutrophil elastase after 8 weeks of treatment.³⁴ Serum and sputum ECP were both reduced after treatment with clarithromycin and roxithromycin.^{37,46}

FeNO is increasingly used as a biomarker of inflammatory activity in asthma and a measure of response to therapy.

Three randomised trials used FeNO as an outcome measure all demonstrating a small and non-significant reduction in response to treatment with 12 weeks of azithromycin (-1.94 (95% CI -5.97 to 2.10) ppb ($p=0.34$)),^{31,26} weeks of azithromycin (MD -1.6 ppb ($p=0.52$))³⁰ and 16 weeks of clarithromycin (-4.6 (SE ± 4.2) ppb ($p=0.5$)), respectively.³⁵

While there is considerable variation in study populations, treatment regimens and outcome measures, the overall picture is that macrolides do reduce airway inflammation in asthma. Further work is needed to clarify if this translates into clinically relevant improvements for patients and to determine which inflammatory biomarker may be of most use in determining response to treatment.

Bronchial hyper-responsiveness

Bronchial hyper-responsiveness has been used as an outcome measure in a number of studies of macrolide therapy in asthma^{31,37,46} to provide proof of physiological effect and potential explanation for improvement in other clinical outcome measures. The studies confirm that macrolide therapy does result in improvements in bronchial hyper-responsiveness

Table 5 Comparison between the AZISAST and AMAZES trials

	Population	Intervention	Follow-up	Patients intervention/control	Primary outcomes
Brusselle et al (AZISAST) ³⁰	18–75 years GOLD step 4/5 >1000 μg fluticasone or equivalent 2 exacerbations requiring OCS in past 12/12 FeNO in normal limits	Azithromycin 250 mg thrice weekly	26 weeks	109 55/54	Exacerbation rate
Gibson et al (AMAZES) ⁴⁰	18 years or older Diagnosis of asthma (postbronchodilator reversibility >12%/airway hyperresponsiveness or PEF variability >12%) Partial loss of asthma control—ACQ ≥ 0.75	Azithromycin 500 mg thrice weekly	48 weeks	420 213/207	Exacerbation rate

measured by methacholine challenge test (PC20/PD20). Two studies were specifically designed to assess bronchial hyper-responsiveness as a primary outcome.^{37,48} When pooled, they demonstrated a 1.99 (95% CI 0.46,3.52 ($p=0.011$)) SMD improvement in methacholine response. A second meta-analysis of five studies demonstrated an improvement of 0.9 (95% CI 0.5,1.75 ($p=0.04$)).³⁶

Other studies demonstrated varying magnitudes in the degree of improvement seen, likely related to differing macrolides, treatment dosages, duration of treatment, study populations and measurement differences.^{31,35,37,46,48} While these findings support a physiological mechanism of action of macrolides through a reduction in airway inflammation and bronchial hyper-responsiveness, there seems to be a lack of clear correlation between the degree of improvement seen and any corresponding improvement in clinical outcomes. This requires further investigation in future trials.

Microbiology

Five studies specifically reported the impact of oral macrolide therapy on microbiological outcomes. Black et al conducted an RCT of 6 weeks of roxithromycin versus placebo in 232 people with asthma and raised IgG/IgA antibody titres to *Chlamydia pneumoniae*.²⁹ This demonstrated a reduction in IgG antibodies, but not IgA in response to treatment; but with no clinically significant changes in other outcome measures. Hahn et al demonstrated that high IgA but not IgG antibodies to *C. pneumoniae* were significantly associated with more severe asthma symptoms at the end of follow-up.³³ Azithromycin resulted in improvements in IgA antibodies regardless of whether IgA antibody levels were high or low at the start of treatment.³³

Sutherland et al attempted to conduct a PCR-stratified RCT based on PCR positivity for *C. pneumoniae* or *Mycoplasma pneumoniae*.³⁵ Due to lower than anticipated numbers of PCR-positive participants, the two arms could not be successfully matched in number, but comparison of the two groups showed no significant differences in outcome between PCR positive ($n=12$) and PCR negative ($n=80$) after treatment with 16 weeks of clarithromycin.³⁵

The AMAZES study monitored a subgroup of study participants for emergence of antimicrobial resistance to azithromycin within serial sputum samples over the 48-week study period.⁴⁰

At the study end, resistance to macrolides was found in 19/39 (48.7%) receiving azithromycin and 12/42 (28.6%) receiving placebo.⁴⁰ AZISAST performed a similar subgroup analysis in 46 participants demonstrating an increase in macrolide-resistant *streptococci* from 47.8% to 87% participants in the azithromycin group and a reduction from 39.1% to 35% of participants in the placebo group.³⁰ Interestingly, the percentage of macrolide-resistant *streptococci* reduced from 73.8% to 45.9% in the 4-week washout period at the end of the study.³⁰ Further analysis of the oropharyngeal microbiome of a subgroup from AZISAST demonstrated a fivefold increase in *Streptococcus salivarius* and corresponding fivefold decrease in *Leptotrichia wadei* during azithromycin treatment. However, azithromycin had little impact on the rest of the microbiota. In keeping with the culture-based microbiology, the microbiome had already returned to pre-treatment levels in 50% participants by the end of the 4-week washout period.⁴⁹

This suggests that chronic macrolide therapy may increase antimicrobial resistance to macrolides. This result has yet to be reproduced in other large studies and the clinical impact of this remains unknown. It is also unclear whether this increase in resistance is temporary or fluctuating. However, it does suggest that monitoring for antimicrobial resistance may be of benefit in those receiving chronic macrolide therapy. Use of breaks in chronic therapy, if the desired clinical outcome is achieved, may be considered to reduce resistance, as is the practice in some bronchiectasis services. Further work is needed to examine this relationship in more depth and determine the clinical impact of increasing resistance rates.

Safety and adverse events

Reporting of adverse events in the majority of studies was of low quality with no specific assessment for the well-documented adverse effects of macrolide therapy in the majority of studies.

However, overall there was little evidence of significant reactions or side effects secondary to macrolide therapy in asthma. The most commonly reported side effects were gastrointestinal, including nausea and abdominal pain. In the meta-analysis performed by Reiter et al, a significantly increased risk of nausea was seen in those receiving

macrolide therapy.⁴¹ Black et al also showed that 12.4% (13/105) of the roxithromycin group developed nausea compared with 4.5% (5/112) of the placebo group.²⁹

The AMAZES and AZISAST trials specifically assessed and reported adverse events as part of the planned study protocols.^{30,40} In AMAZES, the overall serious adverse event (SAE) rate in the azithromycin group was 7.5% (16/213) compared with 12.8% (26/203) in the placebo group.⁴⁰ Gastrointestinal side effects were more common in those on azithromycin compared with placebo—diarrhoea (33.8% (72/213) vs 19.2% (39/203)) and abdominal pain (17.8% (38/213) vs 14.8% (30/203)).⁴⁰ QTc prolongation was not seen more commonly in the azithromycin group with 0.5% (1 participant) of each group developing ECG changes during the study.⁴⁰ There was also no difference in the rates of tinnitus (0.9% (2/213) vs 1% (2/203)) or hearing loss (2.8% (6/213) vs 3.4% (7/203)) seen.⁴⁰

In AZISAST, the SAE rate was identical in both placebo and azithromycin groups (11%).³⁰ Discontinuation of treatment was more common in the placebo group (9% (5/54) vs 4% (2/55)). Diarrhoea, nausea and abdominal pain were also more common in the placebo group. Two participants in the azithromycin group developed abnormal liver function tests, but the severity of this was not reported. No participants reported any change in their hearing.³⁰

Overall, it appears that macrolides are well tolerated in people with asthma, although the quality of evidence is low and inclusion of formal assessment for adverse events should be included in future studies. There is a slightly higher incidence of gastrointestinal side effects which did not lead to cessation of treatment. Warning of the possibility of these side effects developing should be given to patients on initiation of treatment. There is insufficient evidence on the frequency of other adverse events specifically QTc prolongation, liver function abnormalities and audiological changes to make a formal recommendation on screening for these events. In general, participants with evidence of QTc prolongation or hearing loss were excluded from study populations further limiting the applicability of this evidence to the wider asthma population.

Outcome weighting

In the creation of this guideline, a set of key outcome measures in relation to macrolide therapy in management of respiratory disease were determined. However, this guideline's scope covers a spectrum of respiratory disease and the importance of individual outcome measures within each disease area varies. In regards to asthma, the GDG gave importance to those outcomes of most clinical relevance to respiratory physicians managing people with asthma and our recommendations reflect this. The group only made recommendations on these outcomes where the quality of evidence and magnitude of change was deemed sufficient to be of clinical utility. Therefore, recommendations are made in regard to exacerbation reduction, but not in relation to symptoms or quality of life as the changes seen in these outcomes were too small to be clinically important.

The body of evidence in regard to other outcomes, which may be of scientific or physiological relevance, is outlined in the evidence summary below, but no recommendations have been made in areas where the outcome is not used as a clinical endpoint—for example, bronchial hyper-responsiveness.

Evidence summary

Oral macrolide therapy improves quality of life in people with asthma, but changes are small and their clinical significance is uncertain. (Moderate) Treatment with macrolides results in an improvement in asthma symptoms in some patients although this is small in magnitude and may not be applicable to all patients with asthma. (Low) Oral macrolide therapy can reduce exacerbations of asthma in adults (50–70 years) with ongoing symptoms despite >80% adherence to high-dose inhaled steroids (>800 µg/day) and at least one exacerbation requiring oral steroids in the past year. (Low)

Azithromycin given thrice weekly at 500 mg over 48 weeks results in a reduction in asthma exacerbations. (Low)

In some individuals, oral macrolide therapy may result in a reduction in oral steroid dose, but this is not a consistent finding. (Low)

Oral macrolide therapy can result in a small improvement in lung function and PEFR in people with asthma. (Low)

Oral macrolide therapy may reduce airway inflammation in asthma. (Low)

Oral macrolide therapy may reduce bronchial hyperresponsiveness in asthma. (Low) Two studies demonstrated that treatment with oral macrolides (azithromycin) may result in an increase in bacteria within sputum resistant to macrolides, but currently there is no evidence of this adversely affecting clinical outcomes. (Low)

Oral macrolide therapy may result in an increase in gastrointestinal side effects including abdominal pain, nausea and diarrhoea. (Low) There is insufficient evidence to make any recommendation on the impact of oral macrolide therapy on mortality, exercise capacity, disease progression or sputum characteristics in people with asthma.

Recommendations

- Oral macrolide therapy could be considered to reduce exacerbation frequency in adults (50–70 years), with ongoing symptoms despite >80% adherence to high-dose inhaled steroids (>800 µg/day) and at least one exacerbation requiring oral steroids in the past year. This recommendation reflects the population within the AMAZES RCT which represents the highest quality evidence of macrolide therapy leading to a significant reduction in exacerbations. (Conditional)
- Treatment with azithromycin should be considered for a minimum of 6–12 months to assess evidence of efficacy in reducing exacerbations. (Conditional)
- Oral macrolide therapy should not be offered as a way to reduce oral steroid dose; in some individuals, this may result as a consequence of a reduction in exacerbations or symptoms. (Strong)

Good practice points

- ✓ Optimisation of other asthma therapies including establishing good adherence to inhaled therapies should be performed before considering a trial of oral macrolide therapy.
- ✓ Referral to a respiratory specialist or specialist asthma service should be considered prior to initiation of macrolide therapy aimed at reducing exacerbation frequency.
- ✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.
- ✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.
- ✓ Microbiological screening of sputum before and during macrolide therapy may be clinically helpful in patients who are able to expectorate sputum. This would allow monitoring for development of resistance and detect changes in microbial growth to direct appropriate antibiotic therapy if required. However, the resource implications of this approach have not been assessed.
- ✓ If oral macrolide therapy is considered, justification for ongoing treatment should be guided by clinical response based on specific outcome measures including exacerbation frequency, symptoms and quality of life assessed at baseline.
- ✓ A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg thrice weekly) a dose reduction to azithromycin 250 mg thrice weekly could be considered if macrolide therapy has been of clinical benefit.
- ✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.
- ✓ Symptom improvement with macrolide treatment may be minimal and not consistent across all people with asthma. If macrolide therapy is considered for symptom reduction, this should be for a defined period (6–12 months) and stopped if no symptomatic improvement is seen. Use of a validated symptom score, such as the ACQ, may be useful to help make this assessment less subjective.
- ✓ If the desired clinical outcome is achieved the possibility of breaks in therapy may be considered to reduce treatment burden for patients. It is unclear whether this may also reduce antimicrobial resistance rates. See quick reference guide in online supplementary file 1.

Research recommendations

Further research, over a longer period, is needed to investigate the role of long-term macrolide therapy in reducing exacerbations of

asthma. Use of validated scoring systems and creation of a core outcome set should be considered in future trials of macrolide therapy in asthma to allow more accurate delineation of clinical response and comparison between studies.

Head to head comparisons of different macrolide therapy and of differing dose regimens for the same macrolide are required to optimise the use of macrolide therapy in asthma. Research into the discrepancy between significant reductions in inflammation but minimal improvements in clinical parameters is required.

Research into the impact of macrolide therapy in different clinical phenotypes of asthma should be performed in order to assess whether greater benefit is seen in one phenotype over another.

Research into the overlap between asthma and bronchiectasis and the impact of this on response to macrolides may assist in identifying asthma phenotypes which may respond differently to macrolide therapy.

SECTION 5: BRONCHIECTASIS

Introduction

Bronchiectasis is a chronic respiratory condition in which abnormally dilated bronchi are radiologically displayed in patients with a relevant clinical syndrome. These patients suffer from multiple symptoms, including a chronic productive cough, recurrent exacerbations associated with bronchial infection, dyspnoea and fatigue. While patients with cystic fibrosis can have both the radiological changes and the clinical syndrome, the term 'bronchiectasis' generally refers to those who do not have cystic fibrosis and the condition is often referred to as noncystic fibrosis bronchiectasis. Even after the exclusion of cystic fibrosis, a wide range of aetiologies are attributed to bronchiectasis, though a large proportion of cases are described as idiopathic or post-infective.^{50–54} Recent UK data report prevalence rates of 566/100 000 in adult women and 486/100 000 in adult men.⁵³ Patients with bronchiectasis bear a significant burden of morbidity and mortality.^{53,55}

The basic concept for the management of bronchiectasis is to attempt to break the vicious recurrent cycle of chronic bacterial infection, inflammation, impaired mucociliary clearance and structural lung disease.⁵⁶ With the goal of breaking this cycle and the extrapolation of management strategies from cystic fibrosis, it is unsurprising that macrolides have been used to try to improve outcomes in bronchiectasis. As well as having broad antimicrobial effects, anti-inflammatory effects are likely. Studies in patients with bronchiectasis have suggested reductions in Th17 cell responses⁵⁷ and evidence of reduced airway inflammation via measuring markers such as IL8, neutrophil elastase and matrix metalloproteinase-9.⁵⁸ A further attractive mechanism, particularly in a condition where *P. aeruginosa* is an important pathogen, is the inhibition of quorum sensing (a form of chemical signalling between bacteria).⁵⁹

Evidence base

Davies and Wilson described early experiences of using azithromycin in 2004⁶⁰ and subsequent published studies of varying quality, using different regimens, have added to the available evidence. The main body of high-level evidence is based on three RCTs^{61–63} (see table 6). These studies were performed in the Netherlands, Australia and New Zealand and were all placebo controlled. The macrolides used were azithromycin in the Netherlands and New Zealand studies, while the Australian study used erythromycin. Audit data suggest that azithromycin is the preferred macrolide in the UK at present.⁶⁴ The two studies which used azithromycin had different dosing regimens (250 mg daily and 500 mg three times a week). In addition, other studies of lower quality evidence have used other regimens such as azithromycin 250 mg three times a week,^{60,65,66} azithromycin 500 mg twice weekly,⁶⁷ erythromycin 500 mg twice a week,⁶⁸ clarithromycin 500 mg once daily⁵⁷ and roxithromycin 150 mg a day.⁵⁸ The lack of consistency in the macrolide regimen used, and the absence of head-to-head comparisons, make the optimum macrolide and dosing unclear.² Also, because none of the studies were longer than a year, the longer-term benefits and risks have not been established. Subsequent to the three RCTs which provide high-quality evidence, meta-analyses have been produced.^{69–71} While this provides pooled data, some lower quality evidence influence the output.^{66,70} A further meta analysis of individual patient data (IPD) from the three main RCTs was published after the completion of literature searches and is referred to below because of the potential importance of its findings.⁷²

Other recent guidance

The BTS bronchiectasis guidelines cover options beyond macrolides when considering long term antibiotic therapy in stable disease.² They recommend macrolides as first choice for patients without *P. aeruginosa* with inhaled gentamicin as a second-line alternative. For patients with *P. aeruginosa*, the BTS guideline recommends inhaled colistin with macrolides as an alternative for those intolerant of inhaled antibiotics. Interestingly, the IPD meta-analysis by Chalmers et al suggests that macrolides are effective in patients with and without *P. aeruginosa*.⁷² In addition, the BTS guideline recommends a starting dose of azithromycin of 250 mg three times a week to minimise side effects. While accepting that side effects are common with macrolides, we note that dropouts from studies due to side effects are rare and the strongest evidence of efficacy lies with higher dosing regimens. We suggest a pragmatic starting regime of azithromycin 500 mg three times a week or 250 mg daily in patients with bronchiectasis. However, if there is a patient history of drug intolerances, it would be sensible to start at the lower dose of 250 mg three times a week.

A NICE guideline was published in 2018 addressing acute exacerbations in bronchiectasis.⁶ With regards to preventing exacerbations, the document recommends the consideration of prophylactic antibiotics in people with repeated exacerbations.

The guidance is less specific on which antimicrobials to use and what a significant exacerbation rate is. However, both the NICE and BTS documents advocate specialist input.

Quality of life

QOL data were collected from the three main RCTs and consequently there is high-level evidence available. While pooled data are also available, there are limitations of these data due to the influence of data of lower quality.⁶⁶ The studies with the highest quality of evidence used the SGRQ to assess quality of life and any effect seen does not appear to be large. The BAT study did find a significant difference between treatment and placebo, with a reduction of -12.18 points after 1 year of treatment and a reduction of -4.12 in the placebo group ($p=0.046$).⁶² A change of 4 points is considered clinically significant. In the treatment group, 64% achieved this at 1 year while 46% did in the placebo group. While the other two main RCTs did not show a statistically significant improvement in SGRQ, the results from the BAT study should not be viewed as being inconsistent. In the EMBRACE study, 6 months of treatment failed to demonstrate a statistically significant difference though there was a trend towards benefit (-5.17 vs -1.92, 95% CI -7.21 to 0.72).⁶¹ Similar findings were also seen in the BLESS study with 48 weeks of therapy.⁶³ This lack of clear effect may be due to a lack of sensitivity of the SGRQ for this type of therapy. Other studies have reported significant improvements in quality of life; however, the open-label nature or lack of a placebo group means they are of considerably lower quality of evidence.^{60,66} Metaanalysis data did suggest a benefit with a change of -5.39 in the SGRQ; however, these data were influenced by a large change in a study of lower quality.^{69,70}

On the basis of the current high-quality evidence, it appears that to obtain a significant improvement in quality of life, a long course of therapy may be required. On the basis of the BAT trial, this may need to be for a year. It is unclear what the impact of therapy beyond 1 year is. As the only high-quality evidence that suggests an improvement in quality of life is the BAT trial, the dosing regimen of azithromycin 250 mg once a day carries the best evidence for achieving this outcome.

Symptoms

The prospective collection of symptom scores in RCTs has allowed the accumulation of some high-level evidence with regards to symptoms. This has been described in various ways including the symptom component of the SGRQ, the Leicester Cough Questionnaire and the lower respiratory tract infections—visual analogue scale (LRTI-VAS). The EMBRACE study demonstrated an improvement in the symptom component of the SGRQ with a difference in change from baseline of -6.7 (95% CI -13.37 to -0.04).⁶¹ The BLESS study suggested a similar benefit, with a treatment effect of -5.3 reported; however, this did not reach statistical significance (95% CI -12.6 to 2.1).⁶³ There was also no statistically significant change found in the Leicester Cough Questionnaire (LCQ). The BAT study used the LRTI-VAS and described a larger benefit in symptom improvement in those receiving treatment than those receiving placebo ($p=0.047$).⁶² While not unanimous, there does appear to be some evidence of benefit with regards to symptoms, and inconsistencies may in part be due to differences and weaknesses in the scoring systems.

Exacerbations

Due to the three main RCTs using exacerbations as a primary endpoint and the subsequent meta-analyses, there is high level evidence which is in favour of using long-term macrolides to reduce exacerbations in bronchiectasis.^{61–63,69–71} As in other respiratory conditions, there is variability in the interpretation of what exactly constitutes an exacerbation. A consensus definition has been published; however, this was subsequent to the important studies in this field.⁷³

The previously mentioned three principal RCTs described benefit for this outcome when macrolides were used for between 6 and 12 months.^{61–63} The BLESS study described an incidence rate ratio of 0.57 (95% CI 0.42 to 0.77) when compared with no intervention.⁶³ The BAT study reported an absolute risk reduction of 33.5% (95% CI 14.1% to 52.9%).⁶² Of interest in this study, there was an improvement in median number of exacerbation from 5 to 2 in the placebo group. Over a 6-month period, the EMBRACE study identified a rate ratio of 0.38 between the treatment group and the placebo group (95% CI 0.26 to 0.54).⁶¹ It is important to note that the EMBRACE study continued for a further 6 months after stopping the intervention and these benefits were maintained. However, it should also be noted that this study provided two definitions of 'exacerbations' and the results were not consistent, and that there was a higher baseline exacerbation rate in the control group. The meta-analysis data are consistent with an improvement in exacerbation rates.^{69–71}

For macrolides to be used to reduce exacerbations, there needs to be a relevant exacerbation rate at baseline to consider when implementing this therapy. There were different entry criteria for the main trials with regards to baseline exacerbation rates. While entry into the EMBRACE study required just a single exacerbation for study recruitment, the mean exacerbation rate in the preceding year was over three (3.34 in treatment group and 3.93 in control group). In the BLESS and the BAT studies, two and three exacerbations were required, respectively, in the preceding year. In the BLESS study, approximately a third had five or more exacerbations in the preceding year, but it is unclear what the mean or median baseline exacerbation rate was. In the BAT study, the median baseline exacerbation rate was 4 (and 5 in the control group). In light of the baseline exacerbation rates in these trials, and three or more exacerbations being a marker of disease severity,⁷⁴ a threshold of three or more exacerbations per year seems appropriate as a guide. It should be acknowledged that the afo-

Table 6 Three main randomised controlled trials of macrolides in bronchiectasis

	Country	Population	Intervention	Follow-up	Patients intervention/control	Primary outcome (exacerbations)
EMBRACE Wong	New Zealand	Mean age of 60 At least one exacerbation requiring antibiotics in last year HRCT-defined bronchiectasis	Azithromycin 500 mg three times a week	6 months	141 71/70	Exacerbations in first 6 months: 0.59 (treatment group) vs 1.57 (placebo group) $p<0.0001$
BAT Altenburg	Netherlands	Mean age of 62 years At least 3 LRTIs treated with antibiotics in the last year A sputum culture isolating a respiratory pathogens in the last year Bronchiectasis defined by HRCT or bronchography	Azithromycin 250 mg daily	1 year	83 43/40	Exacerbations in 52-week treatment period: 0.84 (treatment group) vs 2.05 (placebo group) $p<0.001$
BLESS Serisier	Australia	Mean age of 62 At least two exacerbations requiring antibiotics in the last year Daily sputum production Clinically stable for at least 4 weeks. HRCTdefined bronchiectasis	Erythromycin ethylsuccinate 400 mg twice daily	48 weeks	117 59/58	Annualised exacerbation rate: 1.29 (treatment group) vs 1.97 (placebo group) $p=0.003$

rementioned IPD meta-analysis that has followed the literature search for this guideline performed multiple subgroup analyses including for different exacerbation rates. One of these subgroups was those with a preceding exacerbation rate of less than this threshold (ie, 1 or 2 per year). While this group was small (37 receiving macrolides vs 36 receiving placebo), there appeared to be a benefit with regards to exacerbations, but a trend towards decreased QOL. It is conceivable that the benefits of macrolides may be outweighed by side effects in those with lower exacerbation rates. This subgroup require further study.

While out of keeping with the BTS Bronchiectasis Guideline and some UK respiratory clinicians' current practice, the regimens used in the three main RCTs (azithromycin 250 mg daily, azithromycin 500 mg three times a week and erythromycin ethylsuccinate 400 mg twice a day) have the greatest supportive evidence of benefit.

The BTS bronchiectasis guideline suggest a lower starting dose (azithromycin 250 mg three times a week) noting the dose-related nature of side effects. Withdrawals due to side effects in the three main studies were, however, rare. It would seem sensible to start at the higher dose (azithromycin 500 mg three times a week or 250 mg daily) unless there is a history of previous drug intolerances.² As well as variable dosing regimens, variable durations of therapy have also been studied. The highest quality studies used macrolide therapy for 6 or 12 months. While it is conceivable that it continues to provide benefit, there is no evidence either in favour or against the prolongation of therapy beyond 12 months.

Exercise capacity

Exercise capacity was measured by a 6 min walk test in both the BLESS and the EMBRACE studies.^{61–63} This provides some high-level evidence via objective measures with blinded subjects and investigators. In neither study was there statistical evidence of benefit or harm from therapy. In addition, the activity component of the SRGQ was reported in the EMBRACE study⁶¹ and no impact on this outcome was seen. On the basis of this evidence from two studies, there is no indication that macrolides influence exercise capacity or tolerance.

Sputum characteristics

Sputum production is a common occurrence in many patients with bronchiectasis and is considered a significant issue by patients.⁷⁵ There is, however, no high-quality evidence with regards to the effects of macrolide therapy on sputum. There is moderate level evidence of reduced sputum weight and sputum volume.^{63–70} Estimates of the effect of therapy may be a reduction of approximately 11 mL per day (95% CI –12.70 to –8.83) based on pooled data.⁷⁰ The BLESS study reported a treatment effect of a reduction of 4.3 g per day.⁶³ It is unclear whether this scale of benefit is important to a patient but could be considered in discussion alongside assessment of other factors such as exacerbation rate when considering therapy.

Safety and adverse events

The evidence base for adverse events is quite variable within the bronchiectasis literature. While QTc prolongation is a potential concern with long-term macrolide use, there is very little evidence with regards to this adverse effect. In the BLESS study, QTc was monitored and one patient was withdrawn due to concerns with regards to prolongation,⁶³ however pre-therapy and post-therapy ECGs suggested that this may not have been a drug-related effect. The EMBRACE and BAT studies did not address this potential adverse event.^{61–62} An adverse impact on hearing is a further concern with macrolides; however, there is also limited evidence for this potential side effect. The BLESS and EMBRACE studies did not assess it, while the BAT study just performed a post-study questionnaire (and did not detect an effect).^{61–63}

There is, however, considerably more evidence in these cohorts for gastrointestinal side effects. The meta-analysis pooled data show high-quality evidence for diarrhoea being an adverse event associated with long-term macrolide use.^{69–71} The frequency of patients suffering diarrhoea was 19.3%–20.6% in the treatment groups compared with 4.1%–4.5% in the placebo groups. There was also high-level evidence for abdominal pain/ discomfort when reported in the BAT study (18.6% vs 2.5%, RR 7.44) and meta-analysis data (OR 6.97).^{62–71} Despite these gastrointestinal side effects, meta-analysis data assessing for withdrawal from studies due to side effects did not reveal any differences between those on macrolide or placebo (OR 1.18, 95% CI 0.33 to 4.19).⁶⁹

While not a patient-centred outcome, high-quality evidence from the BLESS study reports increased micro-organism resistance.⁶³ Further moderate level evidence was also added from the BAT study, though not the EMBRACE trial where routine testing was not performed.^{61,62} In the BLESS study, there was a significant increase of macrolide resistance in commensal *oropharyngeal streptococci* with erythromycin use (27.7% vs 0.04%, $p < 0.001$).⁶³ The BAT study provided a significant amount towards the meta-analysis data and in the pathogens that were tested for macrolide sensitivity, 88% became resistant compared with 26% in the placebo group.^{62–69} At present, there is no evidence that the resistance seen either does or does not have an impact on clinical outcomes.

Outcome weighting

The available data allow assessment of the pre-specified outcomes with varying levels of evidence. Certain outcomes were excluded from our final assessment and recommendations. These included lung function, hospital admission rates, disease progression and death. Lung function was excluded despite available data, as the guideline group did not feel it is a useful measure when taken in the context of the current evidence. The trials were of too short a period for a meaningful change in lung function to be elicited despite statistically significant outcomes. For example, metaanalysis data from five studies described a statistically significant greater improvement of FEV₁ of 0.02 L (mean weighted difference).⁷⁰ This was not considered a clinically meaningful change for an individual patient. Hospital admission rate data were available; however, due to such low incidence rates for this outcome in the three RCTs which reported it, no recommendations are made for this outcome.^{61–63} The outcomes of disease progression and death are not commented on due to a lack of data. The outcomes of QOL, symptoms, exacerbation rates, exercise capacity, sputum characteristics and adverse events were all considered 'important' in the GRADE process.

Evidence summary

There is evidence of an improvement in QOL as measured by SGQR when azithromycin 250 mg daily is used for 1 year (High). Other high-quality studies with other dosing regimens showed a trend towards benefit but not a statistically significant benefit. Meta-analysis data reported a benefit but there are concerns regarding the inclusion of a study of lower quality (Low). There is evidence from high-quality studies of improvement in symptom scores; however, inconsistency exists which may be due to different scoring systems being used. (Moderate) Long-term macrolide treatment reduces exacerbations in bronchiectasis. (High)

When using macrolides to reduce exacerbation rates, the dosing regimens with the greatest supportive evidence are azithromycin 250 mg daily, azithromycin 500 mg three times a week and erythromycin ethylsuccinate 400 mg twice a day. (Moderate) Studies with other dosing regimens, including azithromycin 250 mg three times a week (as pragmatically suggested in the BTS Bronchiectasis Guideline), have also reported a reduction in exacerbation, but have a lower evidence base. (Low) The studies with the greatest evidence for reducing exacerbations used therapy for a minimum of 6 months. (High) The impact beyond 12 months is unknown.

There is evidence for a reduction in exacerbations over 12 months when therapy is used for 6 months and then not for the subsequent 6 months. (Moderate) It is unknown what the impact is of subsequently recommencing. Long-term macrolide therapy is not associated with improved exercise capacity. (High)

Recommendations

Long-term macrolide therapy may reduce sputum volume and weight. (Moderate)

Long-term macrolide therapy is associated with diarrhoea and with abdominal pain. (High)

Long-term macrolide usage can result in increased antimicrobial resistance. (High) It is unknown if this has a clinical impact.

Recommendations

► Long-term macrolide treatment could be offered to reduce exacerbations in those with high exacerbation rates (ie, 3 or more per year). (Strong)

► The dosing regimens with the greatest supportive evidence, when using macrolides to reduce exacerbation rates, are azithromycin 500

mg three times a week, azithromycin 250 mg daily and erythromycin ethylsuccinate 400 mg twice a day. A starting dose of azithromycin 250 mg three times a week could be used to minimise side-effect risk with subsequent titration according to clinical response. (Conditional)

► When using macrolides to reduce exacerbation rates, therapy should be offered for a minimum of 6 months. (Strong)

► Macrolides can be considered with the aim of improving QOL but may require a long period of therapy (eg, 1 year) for significant effects. (Conditional)

Good practice points

✓ Therapies should be optimised in accordance with BTS Bronchiectasis Guidelines before considering long-term macrolide therapy (eg, airway clearance techniques and attendance at pulmonary rehabilitation courses).

✓ Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.

✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.

✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance. Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. When evaluating for NTM infection, macrolides should not be used for 2 weeks before microbiological testing.

✓ Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for bronchiectasis.

✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.

✓ Subsequent follow-up at 6 months and 12 months should determine whether benefit is being derived from therapy. If there is no benefit, treatment should be stopped.

✓ Even if benefit is seen, consideration should be given to stopping treatment for a period each year, for example, over the summer. Such a drug holiday may help with reducing the development of resistance while maintaining efficacy because the vicious cycle has been broken. See quick reference guide in online supplementary file 1.

Research recommendations

Long-term studies of microbiological impact of prolonged macrolide therapy. Head-to-head comparison of different dose regimens for the same macrolide (eg, 250 mg three times a week of azithromycin vs 500 mg three times a week). Head-to-head comparisons of different macrolides (eg, azithromycin vs erythromycin). Prolonged studies of benefit and risk beyond 12 months of use.

Studies assessing the effect of macrolides following reintroduction of therapy after a break. Use of bronchiectasis specific QOL measures in macrolide trials.

Comparison of outcomes in patients with different baseline exacerbation rates when treated with macrolides. Comparison of outcomes in patients with different baseline microbiological culture/microbiome profiles when treated with macrolides.

Comparison of outcomes in patients with different baseline QOL scores when treated with macrolides. Comparison studies of long-term macrolides to other oral or inhaled prophylactic regimens.

Studies looking into the benefits of combined macrolide and inhaled antibiotic regimens.

SECTION 6: COPD

Introduction

COPD is a progressive, inflammatory disease of the airways, characterised by ongoing development of non-reversible airflow limitation and acute episodes of exacerbation. Acute exacerbations are described as episodes of acute worsening of respiratory symptoms that necessitate a change in regular medication.⁷⁶ The natural disease course, health-related QOL, hospital admissions and mortality associated with COPD are influenced by acute exacerbations.⁷⁷ In addition,

acute exacerbations of COPD (AECOPD) are estimated to account for between 50% and 75% of the total costs for COPD treatment.⁷⁸ Treatment interventions effective in preventing acute exacerbations are therefore of significant clinical benefit.

The mechanisms for COPD disease progression are complex and involve inflammatory and immune responses. Neutrophils, IL-17 and IL-23 are considered to play an active role in disease progression while CD8-positive T cells, neutrophils and macrophages mediate chronic inflammatory responses.⁷⁹ Acute exacerbations of COPD are postulated to be caused by bacteria or bacteria in combination with viral infection in up to 50% of cases.⁸⁰ Macrolide antibiotics possess both anti-inflammatory and antibacterial effects and are therefore an important potential treatment strategy to prevent AECOPD.

The potential mechanisms of action and clinical implication of long-term macrolide antibiotic therapy in COPD have been described and reviewed in several studies.⁸¹ Table 7 summarises the potential effects of macrolides on disease modulators in COPD. evidence base

To confirm the hypothesis that macrolide antibiotics are an effective treatment strategy in COPD to prevent acute exacerbations and possibly modify disease progression, several studies have been conducted yielding varied results. The evidence base for effectiveness of macrolide antibiotics in this context is compromised by the significant heterogeneity in populations investigated, intervention (type, dose and duration of macrolide), definition of outcomes measured and lack of phenotyping COPD to identify subgroups most likely to respond.

Six meta-analyses were identified in addition to the published ERS/ATS Guideline on Prevention of COPD exacerbations.⁸²

Nine RCTs were reviewed and included in the guideline. The COLUMBUS trial published in 2014⁸³ and the small RCT by Simpson et al⁸⁴ were included in data analysis of one of the meta-analysis and the ERS/ATS guideline.⁸² Table 8 illustrates the matrix of evidence reviewed, all RCTs and meta-analyses published since 2000 with evidence included in meta-analysis.

Randomised trials excluded

The Cochrane review assessing prophylactic antibiotic therapy for COPD included in the pooled analysis the RCTs performed by Sethi and colleagues⁸⁵ in 2010 (pulsed moxifloxacin 400 mg once a day for 5 days every 8 weeks) and Mygind and colleagues⁸⁶ in 2010 (pulsed azithromycin 500 mg 3 days a month for 36 months). The scope of this guideline does not include pulsed doses of quinolone antibiotics, and this study was not included in the data synthesis. Mygind's (2010) unpublished conference abstract with limited access to data on randomisation, allocation and incomplete outcome data could not be included in analysis of the evidence due to the risk of bias. Shafuddin and colleagues published a three-armed RCT in 2015, comparing usual care, roxithromycin and

Table 7 Potential effects of macrolides in COPD

Macrolide action	Proposed mechanism of action in Copd
Antimicrobial	► Direct antimicrobial action against bacteria commonly associated with exacerbations in COPD (<i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>, <i>Streptococcus pneumoniae</i>, <i>Chlamydia pneumoniae</i> and <i>Mycoplasma pneumoniae</i>) ► Indirect antimicrobial action through inhibition of bacterial quorum sensing
Reduce airway inflammation	► Reduce adhesion molecule expression by epithelial and endothelial cells (ICAM-1, V-CAM-1) ► Modulates pro-inflammatory cytokine release (IL-1, IL-6, IL-8, TNF-α) ► Inhibits signalling pathways (AP-1 and NK-kB transcription factors) ► Influences Toll-like receptor expression and activity
Mucus production	► Antibacterial action inhibits bacterial induced MUC5AC production ► Downregulates protein secretion and expression of MUC5AC mRNA ► Inhibits chloride secretion
Innate immunity	► Macrophages: enhance phagocytosis and monocyte–macrophage differentiation and reduces metalloproteinase production ► Neutrophils: reduce chemotactic response, elastolytic activity and tissue accumulation. Inhibits superoxide anion production. Enhances superoxide dismutase activity
Adaptive immunity	► Lymphocytes: inhibit pro-inflammatory cytokine production and increases apoptosis ► Dendritic cells: modulate pro-inflammatory cytokine production
Prokinetic in GI tract	► Reduce gastro-oesophageal reflux and microaspiration leading to airway inflammation

This table 7 adapted from Blasi et al.⁸¹

Table 8 Matrix of evidence analysed for COPD

RCT → Meta-analysis ↓	Albert et al ⁹³	He et al ⁹⁷	Blasi et al ⁹⁸	Seemungal et al ¹⁰¹	Banerjee et al ⁹⁶	Suzuki et al ¹⁰²	Uzun et al ⁸³	Simpson et al ⁹⁴	Berkhof et al ⁹⁴
Donath et al ²²⁵	●	●	●	●	●	●			
Herath and Poole ²²⁶	●	●	●	●	●	●			
Simoens et al ²²⁷	●	●	●	●	●	●			
Yao et al ²²⁸	●	●	●	●	●	●			
Lee et al ²²⁹	●	●	●	●	●	●			
Ni et al ¹⁰⁰	●	●	●	●	●	●	●	●	●
Wedzicha et al ⁸²	●			●	●		●		

roxithromycin/doxycycline combination. Roxithromycin is not available in the UK, and this therefore prevents generalisability of the evidence, so on this basis, the study was excluded.⁸⁷

Cohort studies

Several retrospective cohort studies were identified, with the largest two (Pomares et al and Yamaya et al) including a total number of 326 patients.^{88–89} The quality of evidence in reporting exacerbations and QOL was deemed poor due to the risk of selection and attrition bias.

Included studies

Based on the aforementioned appraisal of evidence, the included studies for recommendations in this guideline were focused on RCTs and systematic reviews as demonstrated in the evidence matrix (table 8). The RCTs demonstrated significant heterogeneity (in terms of intervention, population and outcomes), and therefore recommendations are limited by uncertainty in the evidence base for a specified intervention. Table 9 demonstrates the trials with variation in detail.

Other recent guidance

GOLD 2019

In patients with COPD optimised with inhaled therapy who are still experiencing exacerbations, the best available evidence exists for the use of azithromycin, especially in those who are not current smokers. Consideration to the development of resistant organisms should be factored into decision-making.⁹⁰

NICE 2018

Recommends after non-pharmacological and pharmacological optimisation to consider azithromycin (usually 250 mg three times a week) for people with COPD more prone to daily sputum production if they have stopped smoking and have more than four exacerbations per year, prolonged exacerbations or exacerbations resulting in hospital admission.⁷

ERS/ATS recommendation

Patients with COPD with moderate to very severe airflow obstruction (post-bronchodilator FEV₁/FVC <0.70 and an FEV₁% predicted of <80%) and exacerbations despite optimal inhaled therapy, treatment with a macrolide antibiotic to prevent future exacerbations is suggested as a conditional recommendation.⁹

Cochrane systematic reviews

Prophylactic antibiotics for patients with COPD that included macrolide therapy found for every eight participants treated, one person would be prevented from suffering an exacerbation. Not all the antibiotic regimens had the same impact on exacerbations, with results suggesting that antibiotics. Prescribing off-label given at least three times per week may be more effective than pulsed antibiotic regimens.¹⁰

Symptoms and QoL

Health status measurement is a standardised and objective means of quantifying the impact of disease on patients' daily life, health and well-being. Health status questionnaires usually address emotional and psychological effects of the illness as well as the physical. The St George's Respiratory Questionnaire (SGRQ) is validated to measure health impairment in patients with COPD. It is in two parts; Part 1 produces the Symptoms score, and Part 2 the Activity and Impacts scores, which results in a total score.^{91–92} Macrolide therapy (azithromycin) improved health-related QOL in four studies (1323 patients) which used the SGRQ.^{83–84–93–94} There was significant heterogeneity among the studies (I²=97.10%). The Berkhof et al study⁹⁴ assessed QOL in patients with COPD, chronic cough and at least one AECOPD in the previous year. Patients with COPD and chronic cough is a heterogeneous group of patients, but from this single study, patients with more severe cough reported better QOL (LCQ) on macrolide treatment. Three other studies did not include LCQ in the disease-specific impact on QOL and the impact of cough could therefore not be pooled and analysed for these studies.^{83–84–93} The pooled assessment for long-term azithromycin suggests its use improved QOL as measured by the SGRQ total score (MD=−2.12, 95% CI −3.44 to −0.79, p=0.002, I²=0%). Although statistically significant, the results did not meet clinical significant outcome of 4 units as minimum clinically important difference (MCID).⁹⁵

Pooled analysis for the Albert et al 2011 and Uzun et al 2014 studies on QOL (SGRQ) in 491 patients on azithromycin and 498 patients on placebo demonstrated improved total scores (MD 2.18 lower, 95% CI 1.53 lower to 2.82 lower), and in symptoms (MD 3.36 lower, 95% CI 2.42 lower to 4.29 lower), activity (MD 1.82 lower, 95% CI 1.03 lower to 2.62 lower) and impacts (mean difference 2.04 lower, 95% CI 1.28 lower to 2.81 lower).^{83–93} The Albert study had a significant 12-month dropout rate in both intervention (444 completed SGRQ at 12 months of 556 enrolled) and control (453 completed SGRQ at 12 months of 555 enrolled patients) groups, and this may have affected the results.⁹³

Banerjee reported improved health status (SGRQ) at 12 weeks on clarithromycin measured in total, symptom, and impact scores.⁹⁶ Erythromycin 125 mg once daily for 6 months did not demonstrate significant changes in quality of life (SGRQ) at 3 and 6 months.⁹²

Banerjee reported improved health status (SGRQ) at 12 weeks on clarithromycin measured in total, symptom, and impact scores.⁹⁶ Erythromycin 125 mg once daily for 6 months did not demonstrate significant changes in quality of life (SGRQ) at 3 and 6 months.⁹²

Exacerbations

Nine RCTs were identified that reported the effect of long-term macrolide antibiotics on AECOPD. The study entry criteria varied in terms of the number of exacerbations in patients in the year prior to the trial, the severity of COPD and the definition of the severity of an acute exacerbation.

Variations

The COLUMBUS trial⁸³ enrolled patients with at least three exacerbations in the year prior to entering the trial. Blasi et al⁹⁸ reported the number of exacerbations in patients the year before entering the trial as 3.1 (±0.9) and 3.0 (±1.1) in the control and intervention arm, respectively. The largest RCT (Albert et al 2011) included in the entry criteria at least one acute exacerbation in the year prior to trial entry.⁹³ The remainder of studies did not define number of exacerbations prior to entering the trial in the inclusion criteria. There was significant variation in severity of disease of patients enrolled in trials, including reporting of severity of disease and airflow limitation measurements reported as the mean FEV₁ measured in litres or as percentage predicted. Albert et al described severity (GOLD criteria⁹⁹) of patients in the intervention/control arm as follows: GOLD 2 (26%/26%), GOLD 3 (40%/40%) and GOLD 4 (34%/33%).⁹³ Uzun et al included patients as follows: GOLD 1 (4/7%), GOLD 2 (30/27%), GOLD 3 (38/40%) and GOLD 4 (28/22%).⁸³

The use of concomitant medication to treat COPD varied in the trials and appears to correlate with published guidelines at the time of trial recruitment (eg, NICE and GOLD guidelines).^{99–100} Treatment recommended during the studies included sustained release theophylline, inhaled corticosteroids, inhaled anticholinergic and beta adrenergic agents. The studies included in the data synthesis used 14-membered and 15-membered-ring compound macrolide antibiotics. Five studies used azithromycin in doses that varied from 750 mg to 1750 mg a week,^{83–84–93–94–98} erythromycin in two studies (1400–3500 mg per week)^{97–101} and one study used clarithromycin 3500 mg per week.⁹⁶

Table 9 Summary of COPD trials

	Country conducted	Population Mean age: intervention/control COPD intervention/control Required an exacerbation in year before	Intervention	Follow-up on treatment	Patients intervention control	Primary outcome
Albert et al ⁹³	USA	Mean age: 65/66 COPD FEV ₁ %: 39/40 Yes—at least one exacerbation	Azithromycin 250 mg a day	12 months	558/559	Time to first exacerbation
He et al ⁹⁷	China	Mean age: 68.8/69.3 COPD FEV ₁ %: 44.3/42.1 No	Erythromycin 150 mg three times a day	6 months	18/18	Exacerbations airway inflammation
Seemungal et al ²³⁰	UK	Mean age: 66.5/67.8 COPD FEV ₁ %: 49.3/50.6 No	Erythromycin (stearate tablets) 250 mg bd	12 months	53/56	Exacerbations airway inflammation
Suzuki et al ¹⁰²	Japan	Mean age: 69.1/71.7 COPD FEV ₁ L/s: 1.47/1.30 No	Erythromycin (ethylsuccinate tablets) 200–400 mg a day	12 months	55/54	Frequency of common cold and exacerbations
Uzun et al ⁸³	Netherlands	Mean age: 64.7/64.9 COPD FEV ₁ %: 44.2/45 Yes—three or more exacerbations	Azithromycin 500 mg three times a week	12 months	47/45	Rate of exacerbations

Exacerbation rate and number of exacerbations

Seven randomised control studies involving 1614 patients reported the number of acute exacerbations during the period of intervention.^{83 93 94 96 97 101 102} Long-term macrolide therapy was shown in a meta-analysis to significantly reduce acute exacerbations in the intervention group when compared with the comparison group (RR=0.7, 95% CI 0.56 to 0.87, $p<0.01$, I²=66.43%).¹⁰⁰ The Suzuki et al 2001 trial was non-blinded and in appraisal of the study methodology, this raised concerns for bias.¹⁰² Analysis of the remaining six studies continued to show benefit for macrolide therapy over placebo, with a 20% relative risk reduction of AECOPD (RR=0.8, 95% CI 0.72 to 0.88, $p<0.01$).

Eight RCTs reported the rate of exacerbation per patient per year in a total of 1582 patients.^{83 84 93 96–98 101 102} The long-term macrolide group had a significant reduction in the rate of exacerbations (RR=0.58, 95% CI 0.43 to 0.78, $p<0.01$, I²=67.8%). The recent published ERS/ATS guideline pooled data for studies that included treatment for 12 months and excluded the Suzuki trial¹⁰² (due to risk of bias, non-blinded study as described above) and demonstrated a reduced rate of AECOPD (RR=0.76, 95% CI 0.68 to 0.86).⁸²

Data analysis demonstrated no significant difference in exacerbation rates at 3 months; it is recognised that these studies were likely underpowered to demonstrate effect size. Banerjee et al reported the effects of clarithromycin for 3 months in 67 patients (RR=3.27, 95% CI 0.53 to 20.18, $p=0.2$)⁹⁶ and Simpson et al on 30 patients with azithromycin for 12 weeks (RR=0.38, 95% CI 0.14 to 1.05, $p=0.06$).⁸⁴ The number of exacerbations at 3 months of treatment did not demonstrate significant variation, as reported by Berkhof et al, with azithromycin in 84 patients (RR=0.46, 95% CI 0.18 to 1.18, $p=0.11$).⁹⁴ In contrast, studies reporting exacerbation rates at 6–12 months^{83 93,98} in pooled assessment with azithromycin (1231 patients) demonstrated significant reduction (RR=0.59, 95% CI 0.37 to 0.93, $p=0.02$) and with erythromycin (254 patients) for 6–12 months^{97 101 102} a similar effect (RR=0.53, 95% CI 0.43 to 0.83, $p=0.01$).

Onset of first exacerbation

Macrolide therapy significantly delayed onset of first exacerbation. Pooled data of patients on macrolide antibiotics for 12 months demonstrates a mean 81-day delay in first AECOPD (95% CI 53.3 to 109.8 days longer)⁸² and the study by Seemungal et al in 109 patients with erythromycin for 12 months demonstrated a mean 182 days delay in first AECOPD ($p=0.02$).¹⁰¹ Daily use of azithromycin long term (12 months) was demonstrated in Albert et al (1117 patients) to significantly reduce exacerbation rate (RR=0.83, 95% CI 0.72 to 0.95, $p=0.01$).⁹³

Two studies adopted intermittent dosing regimens (see table 9, Uzun et al⁸³ and Blasi et al⁹⁸) for azithromycin over 6–12 months involving 114 patients demonstrated reduced exacerbation rates (RR=0.41, 95% CI 0.18 to 0.96, $p=0.04$).^{83 98} Using the intermittent dosing regimen with azithromycin over 12 months rather than 6 months, as reported by Uzun et al, appeared to be more effective to reduce exacerbation rate (RR=0.58, 95% CI 0.42 to 0.80, $p<0.01$).⁸³

Subgroups

Han et al published subgroup analysis of the largest RCT (1117 patients) using azithromycin 250 mg a day for 12 months.¹⁰³ There

was no convincing evidence that treatment efficacy was affected by sex, presence of chronic bronchitis, use of oxygen therapy or concomitant COPD therapy. Long-term azithromycin therapy was found to be more effective in older patients (>65 years, relative hazard 0.59, 95% CI 0.57 to 0.74, $p<0.01$) and in patients who stopped smoking (ex-smoker relative hazard 0.65, 95% CI 0.55 to 0.77; smokers relative hazard 0.99, 95% CI 0.71 to 1.38; p value for interaction=0.03).

Severity of exacerbations on macrolide therapy

The impact of long-term macrolide therapy on the severity of exacerbations was not reported in many studies. Seemungal et al showed that macrolide use was associated with a lower median number of exacerbation days.¹⁰¹ The macrolide group reported median exacerbation days of 9 with IQR 6–13 days, and the placebo group had median of 13 exacerbation days with IQR 6–24 days ($p=0.036$).¹⁰¹ There is insufficient evidence to conclude what the impact on severity of AECOPD is in patients on long-term macrolide therapy.

Hospitalisation for aeCOPD

Five studies involving 1424 patients reported on the number of hospitalisations due to acute exacerbations of COPD as secondary outcomes.^{83 93 94 98 101} Pooled data, as reported by Ni et al, did not demonstrate a significant reduction in hospital admissions in patients with AECOPD on macrolide therapy in comparison with the control group (RR 0.89, 95% CI 0.64 to 1.24, $p=0.50$).¹⁰⁰ Albert et al found a non-significant trend towards reduction in the rate of hospital admissions using macrolides,⁹³ whereas Uzun and colleagues found no significant delay in time to first hospitalisation in patients on long-term macrolide therapy.⁸³

The published evidence does not support the use of long-term macrolides in patients with COPD to reduce severity of exacerbations or requirement for hospitalisation due to exacerbation. The studies were underpowered and definition of severity of exacerbations not comparable with pool data.

Lung function tests and disease progression

The natural history of COPD is characterised by progressive airflow limitation and historically, FEV₁ decline has been considered the single most important marker of disease progression.¹⁰⁴ However, data obtained in two different retrospective cohorts have shown that FEV₁ decline is not invariably progressive and FEV₁ is only weakly correlated with patient-related outcomes.^{105 106}

Randomised trials assessing the impact of long-term macrolide treatment in COPD have not reported on disease progression as a secondary outcome. Rate of decline in FEV₁ as single measure is not accurate in the measurement of disease progression, or in assessing the effect of therapeutic interventions in altering the progression of the disease process.¹⁰⁷

Lung function was reported in four studies. Pooled analysis was not possible due to the varied ways in which results were reported. Banerjee et al reported no difference in the intervention and placebo groups after 12 weeks of clarithromycin in spirometry measurements or shuttle walk distance.⁹⁶ Simpson et al reported no difference in FEV₁ reported as percentage predicted with 12 weeks of azithromy-

cin 250 mg a day (30 patients, 15 in each arm).⁸⁴ No difference in FEV₁ after 12 months' treatment with erythromycin study was withdrawn due to 250 mg or placebo was demonstrated by Seemungal and colleagues in patients with COPD.¹⁰¹ No significant changes were shown between groups in post-bronchodilator FVC, FEV₁ or 6 min walk test in patients on azithromycin 500 mg three times a week after 12 months.⁸³ There is no evidence that long-term macrolide therapy results

in improvements, or lessened decline, of lung function parameters in patients with COPD.

Safety and adverse events

Long-term treatment with macrolides has been associated with several adverse effects.¹⁰⁸ The most common side effects relate to the gastrointestinal tract by stimulating gastrointestinal motility through motilin-like activity. Symptoms including anorexia, nausea, vomiting, diarrhoea and abdominal pain were reported in patients with COPD in the studies reviewed. Cessation of treatment due to gastrointestinal side effects were reported in the studies published by Banerjee et al, Suzuki et al, Seemungal et al, He et al and Blasi et al.^{96–98 101 102} Uzun published sideeffect profiles, indicating that diarrhoea was the only event that was higher statistically significantly more frequent in the azithromycin group compared with placebo.⁸³ Albert et al reported hearing impairment in 142 (25%) patients with COPD treated with azithromycin 250 mg a day and in 110 (20%) patients receiving placebo ($p=0.04$).⁹³ A small, but significant difference was seen at 3-month review in audiology measurements (in all four sound frequencies) in the treatment arm.⁹³

Repeat audiology testing demonstrated improvement regardless if azithromycin was stopped or not. The authors postulate too stringent criteria for measurable deficit and over reporting of hearing impairment as explanation. None of the other studies reported on hearing impairment as an outcome. Erythromycin and clarithromycin are both associated with ototoxicity that includes vertigo, hearing loss, deafness and tinnitus.¹⁰⁹ A single patient receiving long-term erythromycin in the Seemungal et al study was withdrawn due to significant tinnitus.¹⁰¹

The recognised side-effect profile associated with macrolide therapy includes allergic reactions, skin eruptions, hepatotoxicity, cardiac arrhythmias and QTc prolongation.^{110–112} These side effects were not reported as adverse events in the studies reviewed based on the trial protocols and exclusion criteria (designed to exclude high-risk patients specifically with regards to cardiac toxicity). Three studies including ²¹² patients reported four cardiovascular events in the treatment arm and two in the control arm ($p=0.43$).^{83 94 97} Albert and colleagues reported the death rate due to cardiovascular events in both the azithromycin and placebo arm as 0.2%.

Pooled analysis of all nine RCTs reviewed demonstrated higher adverse events reported in the intervention group, with gastrointestinal side effects the most commonly reported (OR 1.55, 95% CI 1.00 to 2.39, $p=0.05$).^{84 93 94 96–98 101 102} Albert and colleagues reported only 11/558 patients in the treatment arm on azithromycin that had to stop the treatment due to GI side effects and 6/559 patients in the control group stopped placebo for the same reason.⁹³

Antimicrobial resistance

Macrolide antibiotics have direct antibacterial activity against Gram-positive, Gram-negative and atypical bacteria such as *Legionella* spp, *Mycoplasma* and *Chlamydia* spp. Macrolides inhibit RNA-dependent protein synthesis by reversibly binding to the P-site on the 50S subunit of bacterial ribosomes and inhibit transpeptidation or translocation of nascent peptides.⁸¹ The severity and rate of AECOPD have been linked to both *C. pneumoniae* and *Haemophilus influenzae*.^{113–117} The antimicrobial activity of macrolide antibiotics with possible reduction in bacterial load may explain in part the effect on exacerbation rate seen in clinical trials in patients with COPD. The acquisition of macrolide resistance with long-term low-dose use of macrolide antibiotics remain uncertain in patients with COPD. Seven studies monitored and reported on macrolide antibiotic susceptibility changes during treatment period.^{83 93 94 96–98 101}

Albert et al found only 15% of patients could expectorate sputum after a 3-month period on macrolide therapy.⁹³ Investigators used sputum in patients who could expectorate and nasopharyngeal swabs to report on colonisation and resistance. This study subsequently reported *Staphylococcus aureus* as the most common organism isolated (treat-

ments group 60 (10.7%) vs placebo group 71 (12.7%)) likely due to nasopharyngeal sampling. *Moraxella* spp and *S. pneumoniae* were both isolated and did not show significant difference between treatment and placebo arms in the study. During the 12-month study period, significantly more patients in the placebo group became colonised (172 patients) versus 66 patients in the treatment arm on azithromycin 250 mg a day ($p<0.001$). Newly colonised patients in the treatment group demonstrated significantly higher resistance to macrolide antibiotics 81% compared with 41% in the placebo group ($p<0.001$).

Seemungal et al reported in 109 patients receiving erythromycin 250 mg twice a day over a 12-month period that only one patient developed resistance to *S. pneumoniae*. *H. influenzae* was isolated in 22 of the 109 patients; all of the isolates were found to be resistant to erythromycin.¹⁰¹ At baseline, Uzun et al obtained 22 sputum samples in the treatment group and 20 sputum samples in the placebo group. After a 12-month study period, 51 sputum samples in the treatment group and 57 sputum samples in the placebo group were analysed. This study also reported fewer new colonised patients in the treatment arm, 4 patients versus 12 patients ($p=0.044$). Macrolide resistance was reported in 6% (3 patients) receiving azithromycin 500 mg three times a week and in 24% (11 patients) receiving placebo for the 12-month period ($p=0.036$).⁸³

Banerjee et al and He et al did not observe significant differences in colonisation rate or resistance to macrolide antibiotics, but these studies were shorter in duration, 3 and 6 months, respectively.^{96 97}

In a single-centre, single-blind randomised placebo controlled trial, Brill et al demonstrated, after 3 months of azithromycin 250 mg three times a week, no difference in airway inflammation or bacterial load (0.42log10cfu/mL) in sputum when compared with placebo (0.08 CI 0.38 to 0.54).¹¹

Mortality

In studies where mortality was specifically reported, no significant difference was observed between the control and macrolide groups (RR=0.9, 95% CI 0.48 to 1.69).^{83 93 102}

It should be noted that the included studies all report mortality as secondary outcome measure, and longer-term potential impact on mortality (through for example reduced exacerbations) may not manifest in the 12-month follow-up period which was typical for these studies.^{106 119 120} There is therefore insufficient evidence to indicate a reduction in mortality with the use of long-term macrolides, but no evidence of increased mortality in relation to treatment.

Outcome weighting

The guideline group identified rate of AECOPD, time to first exacerbation, hospitalisation, serious adverse events and mortality as critical outcomes. Important outcomes identified include QOL, disease progression, lung function tests, airway inflammation and acquisition of macrolide resistance.

Evidence summary

Long-term macrolide treatment showed statistically significant improvement in QOL in patients with COPD as measured by SGRQ, but this does not reach the MCID—4 unit change. (Moderate)

Long-term macrolide antibiotics are effective in reducing the acute exacerbation rate in patients with COPD with high exacerbation rates (ie, more than three exacerbations per year, prolonged exacerbations or exacerbations resulting in hospitalisation). (Moderate)

Treatment courses of 12 months demonstrated the biggest effect size in reduction of exacerbation rate. (Low) The number of hospitalisations was not significantly reduced in patients receiving long-term macrolide therapy. (Moderate) No significant mortality benefit has been shown in 12-month follow-up studies using macrolide therapy, and there is insufficient evidence to demonstrate the effect of long-term macrolide therapy on the mortality in patients with COPD. (Low)

There is no evidence to suggest that long-term macrolide therapy impacts on disease progression or spirometry measurements and exercise capacity measurements. (Low) Insufficient evidence is available on airway colonisation and acquisition of macrolide resistance in patients with COPD receiving long-term, low-dose macrolide therapy. (Moderate)

Recommendations

► Long-term macrolide therapy could be considered for patients with COPD with more than three acute exacerbations requiring ste-

roid therapy and at least one exacerbation requiring hospital admission per year to reduce exacerbation rate. (Conditional)

► Long-term macrolide therapy could be considered for a minimum of 6 months and up to 12 months to assess the impact on exacerbation rate. (Conditional)

Good practice points

- ✓ Non-pharmacological and pharmacological therapies should be optimised prior to considering long-term macrolide therapy. This includes smoking cessation, optimised inhaler technique, optimised self-management care plan, airway clearance techniques and attendance at pulmonary rehabilitation courses.
 - ✓ Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.
 - ✓ For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women, this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests should also be measured.
 - ✓ Patients should be counselled about potential adverse effects before starting therapy including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.
 - ✓ Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. Repeat assessments are recommended with clinical decline or during exacerbations to monitor resistance patterns.
 - ✓ Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for patients with COPD and a CT scan should be considered to exclude a possible diagnosis of bronchiectasis.
 - ✓ A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg thrice weekly), a dose reduction to azithromycin 250 mg thrice weekly could be considered if macrolide therapy has been of clinical benefit.
 - ✓ Liver function tests should be checked 1 month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.
 - ✓ Subsequent follow-up at 6 and 12 months should determine whether benefit is being derived from therapy by using objective measures such as the exacerbation rate, CAT score or QOL as measured by a validated assessment tool such as SGRQ. If there is no benefit, treatment should be stopped.
 - ✓ It is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD unless another antibiotic with potential to affect the QT interval has also been prescribed.
- See quick reference guide in online supplementary file 1.

Research recommendations

Long-term (>12 months) follow-up trials to evaluate impact of long-term macrolide therapy on mortality, antimicrobial resistance, long-term potential cardiac toxicity and disease progression.

Studies to evaluate the impact of short-term breaks in chronic therapy with long-term macrolide antibiotics are needed. Studies phenotyping COPD in large trials where subgroup analysis can potentially identify groups of patients with COPD who will benefit most from long-term macrolide therapy.

Trials investigating head to head the benefits and adverse effects of oral agents that reduce acute exacerbations in patients with COPD (long-term, low-dose macrolides, carbocysteine, roflumilast).

SECTION 7: BRONCHIOLITIS OBLITERANS (INCLUDING POST TRANSPLANTATION)

Introduction

Bronchiolitis obliterans is a condition characterised by subepithelial inflammatory and fibrotic narrowing of small airways within the lung. It occurs following a variety of insults to the lung such as infections or inhaled toxins. It also occurs in the context of systemic diseases such as rheumatoid arthritis and other connective tissue diseases. It can occur as a complication of transplantation of lung or haematopoietic stem cells (HSCT).

The histological correlate is obliterative bronchiolitis or constrictive bronchiolitis.¹²¹

In the context of lung transplantation, bronchiolitis obliterans causing lung function impairment without histological confirmation has been called bronchiolitis obliterans syndrome (BOS). A standard definition of BOS was first developed in 1993¹²² based on changes in FEV₁ following transplantation. The definition has undergone subsequent revisions in 2002¹²³ and in 2014¹²⁴ when the over-arching term of chronic lung allograft dysfunction (CLAD) with subdivisions of restrictive CLAD (restrictive allograft syndrome, RAS) and obstructive CLAD (BOS) were proposed. BOS is common after lung transplantation occurring in over 50% of those surviving more than 5 years. It is less common after HSCT, between 2% and 14% in the first 5 years post transplant. Long-term macrolides have been used both to prevent BOS and to treat BOS when it occurs. Several observational studies have noted a positive response to azithromycin in a proportion of patients with BOS following lung transplantation, especially those with neutrophilic bronchoalveolar lavage results. This has been labelled neutrophilic reversible allograft dysfunction or azithromycin responsive allograft dysfunction distinguishing it from the non-reversible CLAD.

Evidence base

There is a significant body of literature relating to bronchiolitis obliterans occurring in the context of lung or HSCT. In the lung transplantation field, the majority of published studies are case series. There is marked variation between studies in patient groups, concomitant immunosuppressive regimens, choice of macrolide and dosing regimens, and choice of outcome measures making meaningful systematic analysis of the data impossible. In patients with bronchiolitis obliterans complicating HSCT, there are fewer studies, predominantly case series, also with a high degree of variation in populations, background immunosuppressive regimens, macrolide interventions (often in conjunction with other novel therapeutic agents) and outcome measures precluding meaningful systematic analysis.

Macrolides in BoS/CLad following lung transplantation

An International Society for Heart and Lung Transplantation/American Thoracic Society (ATS)/European Respiratory Society (ERS) clinical practice guideline on the diagnosis and management of BOS was published in 2014 following the GRADE approach to develop specific clinical recommendations including the use of azithromycin.¹²⁴ This guideline identified 10 studies (one observational study and nine case series) that described the effects of azithromycin on the lung function of lung transplant patients with BOS. It also identified two observational studies that described the effect of azithromycin on mortality in lung transplant patients with BOS. The guideline recommended a trial of azithromycin (250 mg orally daily for 5 days and then thrice weekly for a minimum of 3 months) for lung transplant recipients who developed a decline in FEV₁ consistent with the onset of BOS. The recommendation was conditional.

There have been two RCTs investigating the role of macrolides in BOS following lung transplantation. Vos et al examined the effect of azithromycin versus placebo for the prevention of BOS following lung transplantation.¹²⁵ Corris et al studied the effect of azithromycin versus placebo in the treatment of patients who developed BOS following lung transplantation.¹²⁶

In the Vos et al single-centre paper, patients who had undergone lung transplantation were randomised to receive either azithromycin, 250mg three times a week (40 patients) or placebo (43 patients) for 2 years in a fully blinded study. Primary end points were freedom from BOS and survival at 2 years. If patients developed BOS on placebo, they were switched to open-label 'rescue' treatment with azithromycin. Patients receiving prophylactic azithromycin were less likely to develop BOS than those on placebo (12.5% vs 44.2%, *p*=0.0017). Overall survival was comparable between groups.¹²⁵ This group of investigators have subsequently published a post hoc analysis of the same patients who were treated for a further year applying the newer CLAD classification system over an extended 7-year period of observation.¹²⁷ The treated patients were less likely to develop CLAD at any stage compared with the placebo patients (28% vs 51%, *p*=0.043). There were also benefits in CLAD-free survival, long-term pulmonary function and functional exercise capacity, but graft loss (re-transplantation and mortality) was similar in both groups (53% vs 40%, *p*=0.27).¹²⁷ In the Corris et al paper, 46 patients with BOS following lung transplantation were randomised to receive either azithromycin, 250 mg on alternate days (23 patients) or placebo (23 patients) over a 12-week study period

in double-blind fashion. The primary end point was change in FEV₁ at 12 weeks. Patients who had a rapid and severe deterioration in lung function were withdrawn from the study and received open-labelled azithromycin. On an intention-to-treat (ITT) analysis, there was no significant difference between treatments in the primary outcome (0.035 L, $p=0.6$). For study completers (16 azithromycin and 17 placebo), there was a significant difference of 0.278 L ($p\leq 0.001$). In addition, 9/23 ITT patients in the azithromycin group had a $\geq 10\%$ gain in FEV₁ from baseline while no patient in the placebo group had $\geq 10\%$ gain in FEV₁ while on placebo ($p=0.002$).¹²⁶ This latter observation, previously noted in other studies,¹²⁸ suggests a subgroup of BOS patients who exhibit a response to azithromycin and is one of the drivers for recommending the re-classification of CLAD following lung transplantation noted above.

Evidence summary

The evidence for macrolides in BOS following lung transplantation covers both prophylactic use to prevent BOS and treatment following the occurrence of BOS. In both areas, there are single RCTs and a number of case series. The overall quality of the evidence is at best modest; however, BOS is a devastating complication of lung transplantation, so any intervention that offers the chance of prevention, reversal or stabilisation is welcome. Longterm macrolide use is a low-risk intervention. On this basis, we can make two recommendations. (Low)

Recommendations

- Low-dose, long-term azithromycin (250 mg thrice weekly) could be considered to prevent the occurrence of BOS post lung transplantation. (Conditional)
 - Low-dose azithromycin (250 mg alternate days for a trial period of 3 months) could be considered to treat BOS occurring in lung transplant recipients. (Conditional)
- macrolides in BoS following hSCT There are a number of case series and one RCT examining the role of macrolides (sometimes in combination with other emerging therapies) in BOS following HSCT. Khalid et al reported prospectively from Saudi Arabia on a series of eight HSCT patients with BOS diagnosed on the basis of lung function and high-resolution CT scanning who were treated with azithromycin for 12 weeks. All patients showed improvement in FEV₁ and all but one in FVC following treatment.

The changes were statistically (FEV₁, $p=0.0052$; FVC, $p=0.0067$) and clinically (FEV₁ 21.6%, FVC 20.6%) significant.¹²⁹ Norman et al described a retrospective, single-centre series of eight HSCT patients in North America with newly diagnosed BOS who were treated with a combination of fluticasone (inhaled), azithromycin and montelukast (the FAM regime) in addition to a more rapid taper in systemic corticosteroids than was normal practice. The intention was to reduce systemic corticosteroid exposure in these patients. Comparison with historical controls (HSCT patients with BOS treated with much higher overall doses of systemic steroids) suggested equivalent efficacy in maintaining lung function.¹³⁰ Jo et al from South Korea, in a retrospective study, described the effect of prophylactic azithromycin in reducing the incidence of BOS in a series of 100 HSCT patients compared with over 1000 similar patients who did not receive prophylactic azithromycin. The incidence of BOS in those who received azithromycin was 12% compared with 6.4% in those who did not. Subsequent multivariate analysis did not suggest that prophylactic azithromycin was associated with the development of BOS.¹³¹

In a multicentre open-labelled prospective study, Williams et al examined the effect of the FAM regimen on new-onset BOS in HSCT patients. The primary end point was treatment failure by 3 months defined as an absolute decline in % predicted FEV₁ of $>=10\%$. Thirty-six patients from 10 centres were studied. Two patients (6%) had treatment failure compared with 40% of historical controls.¹³² The single-centre RCT from Lam et al in Hong Kong compared the effect of 12 weeks' treatment with daily azithromycin, 250 mg, compared with placebo in 22 HSCT patients with BOS. Primary outcomes were changes in QOL (SGRQ) and lung function (FEV₁, FVC and FEF 25–75) measured monthly and 1 month after completion of treatment. The authors reported no change in lung function or SGRQ although the QOL data were analysed in an unusual fashion.¹³³

Evidence summary

The literature for macrolides in BOS following HSCT is limited. There is only one RCT which has significant methodological limitations. The majority of case series are small and half are retrospective. There are differing diagnostic criteria for BOS and in some studies

multiple drugs including azithromycin are used. Several authors comment on the difficulty of performing studies in this patient group where the condition is a rare complication of HSCT (making it difficult to gather high patient numbers) with devastating consequences (making it difficult to justify and recruit to a placebo limb). This situation is discussed in detail in an editorial.¹³⁴ There is insufficient evidence for us to make a recommendation.

Macrolides for other causes of bronchiolitis obliterans

There are no published studies looking at macrolide treatment for other causes of bronchiolitis obliterans. There is a single case report of bronchiolitis obliterans following dust exposure on 9/11 with response to azithromycin¹³⁵ and one recent review article suggested a possible role for macrolides in the treatment of bronchiolitis obliterans associated with rheumatoid arthritis.¹³⁶

SECTION 8: THE USE OF MACROLIDES FOR OTHER RESPIRATORY CONDITIONS

Cough

Chronic cough, defined as a cough lasting more than 8 weeks,¹³⁷ is a very common symptom, with an estimated prevalence in total of 9.6% of the population, with variations according to geographical area from as high as 12.7% in Europe to 4.4% in Asia.¹³⁸ It has been reported as the most common symptom for which patients seek medical attention.¹³⁹ It occurs most commonly in women in the fifth and sixth decades of life, and has been associated with significant impacts on physical and psychological health.^{140–141} The most common causes of chronic cough remain cough variant asthma, postnasal drip and gastroesophageal reflux disease, with around 40% remaining of 'unknown cause' after investigation.¹⁴¹

When an underlying cause of chronic cough is not identified, or when cough is resistant to prolonged treatment of the underlying cause, a number of treatments have been assessed to attempt to reduce cough frequency, reduce symptoms and improve QOL. These include randomised trials demonstrating the utility of low-dose opioids¹⁴² and gabapentin.¹⁴³ Amitriptyline has been trialled (non-randomised) in cough with some success.¹⁴⁴

Macrolides have been used in an attempt to reduce the symptoms or frequency of chronic cough. The rationale for their potential use in chronic cough includes impact on neutrophilic airways inflammation which is raised in some patients with chronic cough,¹⁴⁵ and has been shown to be decreased with use of macrolides,^{34–101} and the potential anti-inflammatory effects of macrolides, independent of their antimicrobial actions.¹⁴⁶

Evidence base

Included studies

The search strategy revealed a total of 10 papers, which included two randomised trials, three review articles, three retrospective studies on sino-bronchial syndrome in far eastern populations, one validation study of a cough tool and one animal study.

Only the two, blinded placebo controlled randomised studies (Yousaf et al 2010 and Hodgson et al 2016)^{147–148} were included in the formulation of this guideline, with other studies rejected on the basis of being out of scope (sino-bronchial syndrome only, validation study, animal study) or irrelevant to the PICO question.

Outcomes and interventions

The outcomes assessed in the two randomised trials were varied, and heterogeneity in the outcomes (and interventions) meant that any form of meaningful data synthesis was not possible. Outcomes included number of coughs/24 hours, change in the LCQ, dose of capsaicin challenge to cause two coughs (C2) or five coughs (C5), Visual Analogue Score 100 mm for cough, number of colony-forming units in sputum for microbiology and cough severity.

Yousaf et al assessed the effect of erythromycin 250 mg once daily for 12 weeks on the primary outcome (log change in 24 hours cough frequency from baseline) in 30 patients,¹⁴⁷ while Hodgson et al assessed the effect of 250 mg azithromycin thrice weekly for 8 weeks on LCQ score (primary) in 44 patients.¹⁴⁸

Evidence summary

Yousaf et al demonstrated no significant difference in cough frequency between the intervention and placebo groups (mean difference in log change of cough frequency 1.1, 95% CI 0.7 to 1.5,

$p=0.59$), despite a significant change in the sputum neutrophil count at 12 weeks, although at other time points no difference was found.¹⁴⁷ Hodgson et al demonstrated no significant difference between placebo and intervention in LCQ, nor for any secondary outcome measurements. A subgroup analysis was conducted (post hoc), identifying a subgroup of responders to azithromycin therapy (ie, those with a concomitant diagnosis of asthma, mean LCQ improvement compared with placebo 5.77; 95% CI 2.75 to 8.79). However, given the small size of this group (18 patients in total) and post hoc nature of the subgroup, it is highly likely that this analysis suffers with bias.¹⁴⁸

Side effects and adverse events

Side-effect profiles were published in both trials; Yousaf et al reported two patient withdrawals on erythromycin 250 mg per day for 12 weeks, one of whom reported dizziness which resolved.¹⁴⁷ Hodgson et al reported one withdrawal on azithromycin due to GI side effects. In the study as a whole, there were no statistically significant differences in side effects between intervention and control group (eight patients with GI side effects in the intervention group vs five in the placebo group).¹⁴⁸

Evidence statements

Long-term macrolide antibiotics are ineffective in improving any outcomes in chronic cough, accepting that only two small RCTs have been conducted (totalling only 72 patients). These outcomes include those proven to be of importance in chronic cough such as the LCQ, number of coughs and 100 mm VAS for cough. (Low)

Recommendations

► Long-term macrolide antibiotics should not be used to manage patients with unexplained chronic cough. (Conditional)

Research recommendation

High-quality, adequately powered randomised trials are needed to assess the effect of macrolides on outcomes of importance in chronic cough.

Organising pneumonia

Organising pneumonia (OP) is a clinicopathological syndrome associated with characteristic patterns on lung imaging and biopsy which represents an aberrant healing response to injury within the small airways and alveolar spaces. CT scanning typically shows patchy consolidation with air bronchograms, typically in subpleural locations, which may appear migratory on serial imaging. Ground glass change, reversed halo (atoll) sign, reticulation or nodules may also be seen. Histological features of OP include fibroblasts and inflammatory cells embedded in extracellular matrix within the small airways and alveoli, often forming polypoid masses known as Masson bodies. OP can occur in a variety of conditions including infection, connective tissue disease, malignancy, following radiotherapy, drug reactions and immunodeficiency. If no cause can be found on exhaustive testing the term cryptogenic organising pneumonia (COP) (previously called bronchiolitis obliterans organising pneumonia) is used. COP is a rare disease (annual incidence ~1:100 000) that presents with breathlessness and cough over weeks or months, often accompanied by fever, myalgia and elevated blood inflammatory markers. Lung function tests typically show restriction and impaired gas transfer. The prognosis of COP is good, particularly when consolidation is the primary pattern on CT. The natural history is spontaneous remission in many untreated cases.¹⁴⁹ In non-remitting or progressive COP, oral corticosteroids have been used often in reported case series.¹⁵⁰ There have been no placebo-controlled trials of steroid therapy, but is believed that there is an autoimmune aetiology in a proportion of cases and that steroids speed resolution. In steroid-responsive cases, relapse may occur after stopping therapy.

Evidence summary

The evidence base for macrolide therapy in OP consists of case reports and small case series totalling fewer than 50 patients.^{151–161} Macrolides were used either first-line in untreated patients or less commonly, as an add-on therapy with oral steroids. When used first-line, no studies described an initial observation period to identify self-resolving disease. Clinical outcome reporting is variable, but overall the published studies report clinical improvement in response to macrolide therapy.¹⁶² The risk of publication bias is high. Because the natural

history of untreated COP is often self-resolution, in the absence of placebo-controlled trials, no conclusions can be made about the efficacy of macrolide therapy. There is insufficient evidence to make a recommendation.

Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB) was defined as a specific clinicopathological entity in the 1960s, being characterised histologically by multiple micronodular lesions consisting of chronic inflammatory cells infiltrating bronchiolar walls.^{163–164} It has almost exclusively been reported in East Asian countries, notably Japan, but also others such as China and South Korea.¹⁶³ Relatively few cases have been diagnosed in Caucasian and other populations.^{163–165}

DPB was one of the first respiratory conditions for which it was identified that a regular macrolide, erythromycin, at a lower dose than usually used in therapy, could be associated with notably improved outcomes for sufferers. This was discovered in the early 1980s, although there has been a paucity of published rigorous and well-designed placebo-controlled trials subsequently to test the hypothesis, with further supporting evidence largely in the form of (usually small) case series and observational studies.^{163–167} The largest published study was retrospective, involving nearly 500 Japanese patients with DPB.¹⁶⁸ These patients were divided into three cohorts on the basis of likely date of diagnosis, which were then compared with respect to outcome. There was a statistically significant survival advantage ($p<0.0001$) to being in the third cohort and thereby diagnosed between 1985 and 1990.

This was ascribed as being directly related to when the beneficial role of low-dose erythromycin in DPB had first been reported.¹⁶⁸ To provide support for this, the records of this third cohort of 87 patients were analysed in more detail—and there was a significantly higher survival rate at 5 years of those who were known to have received erythromycin compared with those who had not ($p=0.01$).¹⁶⁸ Moreover, those who had not received erythromycin had a similar 5-year survival rate to those in the first cohort, who had been diagnosed between 1970 and 1979, and therefore before the first reports of benefit with such a strategy.^{163–168} DPB case series studies have also shown the effect of low-dose macrolide therapy in controlling clinical symptoms, such as by reducing sputum production, and objectively improving lung function.¹⁶⁷ The benefits of using low-dose macrolide therapy in the setting of DPB have been endorsed by clinical guidelines developed in the Far East.¹⁶³ However, due to the current rarity of this condition in the UK, the GDG felt that it was not warranted for BTS to conduct a comprehensive evidence-based review and develop specific recommendations regarding the role of macrolides in managing DPB.

SECTION 9: SAFETY ISSUES

Gastrointestinal effects

Gastrointestinal (GI) side effects of macrolides have been recognised since the introduction of erythromycin in 1952. Although initially thought to be due to alterations in gut flora, it is now clear that macrolides act through interactions with motilin receptors in the gut.^{169,170} In humans, macrolides potentiate gastric and small bowel motility,^{171–175} increase lower oesophageal sphincter pressure,^{176–177} and influence colonic transit and gall bladder function.¹⁷⁸

The prokinetic effects of macrolides on the GI tract has led to their therapeutic use in conditions characterised by reduced GI motility including diabetic gastroparesis,¹⁷⁹ anorexia nervosa,¹⁸⁰ colonic pseudo-obstruction, postoperative ileus¹⁸¹ and in critical care patients.¹⁸²

GI symptoms are the most commonly reported side effects of macrolides occurring in up to 70% of patients taking erythromycin,¹⁸³ less commonly with clarithromycin and azithromycin. Symptoms include nausea, vomiting, abdominal pain, diarrhoea and anorexia. Commenting on 11 studies of long-term, low-dose macrolide treatment in various chronic respiratory diseases in nearly 1000 children and adults, Altenburg et al²³ found that mild to moderate GI complaints had been reported which hardly ever caused study drug discontinuation. Thus, although GI symptoms are common and predictable, they are rarely sufficiently troublesome to necessitate discontinuation of therapy. Dose reduction may improve tolerability.

Good practice points

✓ Prior to initiating low-dose macrolide therapy, patients should be warned of the possibility of GI side effects.

- ✓ GI side effects may be ameliorated by dose reduction although this may also reduce clinical efficacy.
- ✓ Clinicians should carefully consider the risk-to-benefit balance when considering therapy for those with preexisting GI symptomatology.

Cardiac effects

Macrolide antibiotics, along with a wide range of other pharmacological agents, have the potential to interfere with conduction in cardiac tissue and hence to cause dangerous cardiac arrhythmias and sudden cardiac death.¹⁸⁴ Macrolides can both directly prolong the QT interval¹⁸⁵ and also inhibit the metabolism of other proarrhythmogenic drugs by acting on cytochrome P450 in the liver.

In recent years, there have been reports of an increased risk of cardiovascular death in patients treated with short, oral antibacterial courses of azithromycin¹¹⁰ and of no increased risk of death in a younger group of similarly treated patients.¹⁸⁶ Discussion of these seemingly contradictory findings commented that the group of patients with increased risk exhibited a high level of baseline risk and comorbidity.¹⁸⁷ Factors increasing the risk of malignant arrhythmias with macrolides are well recognised and include age >80, female gender, heart disease, use of other QT prolonging medication, reduced drug elimination, bradycardia, prolonged QT interval before therapy and genetic predisposition.¹⁸⁸ These events are rare; 85 deaths for each 1 million courses prescribed in the increased risk group described above,¹¹⁰ so it is not surprising that such events do not appear in the literature of long-term, low-dose macrolide use.

A helpful review article for the American COPD Clinical Research Network describes a pragmatic approach to risk stratification when considering long-term, low-dose macrolide therapy.¹⁸⁹ The authors combined history taking targeting evidence of heart failure, episodes of hypokalaemia, a family history of long QT syndrome, or use of other medications known to prolong the QT interval together with a pre-treatment ECG and an ECG 1 month after starting therapy. With this approach in a COPD population entering a macrolide trial, 7.1% were excluded on history and 1.6% because of a prolonged baseline QTc. A further 0.8% were withdrawn after developing QTc prolongation with treatment or on placebo. Using such a strategy, exclusions in asthma and bronchiectasis populations are likely to be fewer.

Good practice points

- ✓ Prior to initiating low-dose macrolide therapy, patients should be asked if they have a history of heart disease, previous low serum potassium measurements, a slow pulse rate, a family history of sudden death or known prolonged QT interval. Patients with such a history should not receive low-dose macrolide therapy without careful consideration and counselling of the increased risk of adverse cardiac effects.
- ✓ Prior to initiating low-dose macrolide therapy, a drug history looking for agents that might prolong the QTc interval should be sought (see online supplementary appendices 3 and 4). Patients taking such agents should not receive low-dose macrolide therapy.
- ✓ Prior to initiating low-dose macrolide therapy, an ECG should be performed to exclude a prolonged QTc interval defined as >450 ms for men and >470 ms for women (see methodology in online supplementary appendices 3 and 4). Patients with a prolonged QTc interval should not receive low-dose macrolides.
- ✓ One month after initiating low-dose macrolide therapy, a second ECG should be performed to exclude the development of a prolonged QTc interval. Patients who develop a prolonged QTc interval on low-dose macrolides should stop the macrolide.
- ✓ If any new drug that could potentially prolong QTc time is started or if dose increases are made repeat ECG assessment.

Ototoxicity

Macrolide ototoxicity is well recognised usually causing a dose-dependent, reversible, sensorineural hearing loss (SNHL).²³ The only systematic review of this topic was published recently¹⁹⁰ including data from three prospective studies. In these studies including 93 patients, 14 (15%) developed SNHL confirmed by audiometry following exposure to macrolide antibiotics. All but one recovered on cessation of the drug. Earlier studies of long-term macrolide use for the treatment of mycobacterial infections have also reported reversibility of ototoxicity following either withdrawal^{191 192} or dose reduction¹⁹³ of the macrolide. Albert reported hearing decrements in 25% of a COPD

population (vs 20% in the placebo group) with normal hearing at the outset of 1 year of low-dose azithromycin.⁹³ Hearing subsequently improved in 34% who discontinued treatment, but also in 32% who continued due to protocol errors. Similar proportions of placebo-associated hearing loss also improved with or without drug withdrawal. The authors of this study felt in discussion that their criteria for defining hearing loss were too stringent and that the incidence of hearing decrements were overestimated.

Overall, the literature suggests that for low-dose, long-term macrolide use the incidence of ototoxicity is rare and almost always reversible. It would seem sensible to assess potential recipients for hearing impairment or difficulties with balance prior to initiating therapy.

Good practice point

- ✓ Prior to initiating low-dose macrolide therapy patients should be asked if they have a history of hearing or balance difficulties. Such patients should be made aware of the potential for a further, almost always reversible, deterioration in hearing or balance with macrolide therapy. Patients with pre-existing hearing or balance difficulties who wish to proceed with treatment should be asked to report any change in hearing or balance promptly.

Other side effects

A low rate (1%–5%) of asymptomatic elevation of serum aminotransaminase levels is known to occur with any of the four orally absorbed macrolide antibiotics. The elevation is generally mild to moderate in degree and rarely requires dose modification or discontinuation. More seriously, a cholestatic picture can occur which carries a higher risk of permanent liver damage.^{194 195} Monitoring liver function at the start of therapy seems a sensible precaution.

Good practice points

- ✓ Prior to initiating low-dose macrolide therapy, baseline liver function tests (LFTs) should be checked.
- ✓ LFTs should be checked after 1 month of treatment and then every 6 months thereafter for the duration of therapy.

Prescribing off-label

It is important to be aware that none of the macrolide antibiotics have a product license in the UK for the indication of long-term, low-dose usage as immunomodulatory agents. Their prescription in this context is thus off label. Clinicians should make patients aware of this and follow GMC guidance in this area which states that “decisions should be made in collaboration with the patient by discussing the options with them and ensuring that they have sufficient information about the medicine to allow them to make an informed decision”. An example of an information leaflet used to support such discussions is shown in online appendix 4.

SECTION 10: ANTIMICROBIAL RESISTANCE

Antimicrobial agents are different to other medications, as they can be associated with undesirable consequences not only in the patient receiving the treatment, but also for other individuals - both at the time and potentially at much later dates in the future. Exposure of bacteria to an antibiotic may be associated with subsequent alterations in those bacteria such that they become resistant to its effect. This means that the antibiotic loses its therapeutic value. If the antibiotic exposure, that is, with its associated selection pressure, is stopped such resistant bacteria do not necessarily revert back to being susceptible in future. The encoding mechanism of the bacterial resistance to an antibiotic's effect may be located on mobile genetic elements, such as plasmids or transposons, which will then be inherited by the future progeny of that bacterium, and may also be transferred to other strains of the same species, and indeed to other species. Such mobile genetic elements may carry the gene(s) encoding resistance to the specific antimicrobial agent, or its class, being used; and also resistance mechanisms to other, completely unrelated, antimicrobial agents/classes—that is, conferring resistance to multiple different agents. These resistant bacterial strains can then be transmitted to other individuals or establish persisting reservoirs in the environment.

The resistance mechanism does not need to evolve in the pathogenic organism(s) primarily being targeted by the antimicrobial treatment. Other bacterial species, of low or no virulence, may develop such mechanisms to survive in their antibiotic-exposed milieu, such as the GI or upper respiratory tracts, but may then transmit the

means to other, more virulent, species. The rise in antimicrobial resistance is of national and international concern.^{196–197} Not all bacteria are able to develop resistance to all antimicrobials to which they are naturally susceptible. However, this can then lead to the disappearance of some non-pathogenic commensal, 'good', bacterial species in any exposed microbiome; and their replacement by other organisms which are resistant, either intrinsically or by acquisition, which in turn may lead to subsequent infections. Such a shift in pathogens could include methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, Gram-negative bacilli and yeasts.

These ecologically adverse effects have been termed the 'collateral damage' associated with antibiotic use.¹⁹⁸ The macrolides, such as erythromycin, clarithromycin and azithromycin, inhibit RNA-dependent protein synthesis by bacteria by binding to the 50S ribosomal subunit.¹⁹⁹ Various mechanisms by which bacteria may resist their action have been elucidated, with resistance often being cross-class.¹⁹⁹ Many Gram-negative bacteria, such as *Enterobacteriaceae* ('coliforms'), *Pseudomonas* and *Acinetobacter* species, show reduced permeability of their outer cell envelope to macrolides. Azithromycin is more active in vitro against a range of Gram-negative bacteria than erythromycin. This is thought most likely due to the molecule being able to penetrate such bacterial cells more effectively.²⁰⁰ Organisms, such as *S. aureus* and coagulase negative staphylococci, may have plasmid-mediated macrolide resistance by increased efflux.²⁰¹

The 50S target site may be altered, reducing the binding affinity.²⁰² This has been reported in a wide range of potential pathogens, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Helicobacter pylori* and *Mycobacterium avium* complex.^{199–203} The genetic mutation is mediated by *erm* genes, located either on transposons in the bacterial chromosome or on plasmids. Such resistance may also be associated with resistance to lincosamides such as clindamycin. Resistance may also be conferred by enzymatic inactivation, such as by phosphotransferases in *S. aureus*, *Escherichia coli* and *Nocardia* species.¹⁹⁹

Rising bacterial resistance rates to macrolides have been reported globally. For *S. pneumoniae* isolates, it can vary markedly between countries, ranging from less than 10% to over 90%.²⁰³ Extensive macrolide use provides a strong selective pressure for the spread of macrolide resistance in pneumococci.^{203–204} There is a notable trend for *S. pneumoniae* isolates, which are resistant to penicillin, also to be resistant to macrolides—in the USA, there are reports of 30% of *S. pneumoniae* isolates overall being erythromycin resistant, but virtually 70% of high-level penicillin-resistant isolates also exhibiting erythromycin resistance.^{199–205} However, it should be recognised that the increasing use of pneumococcal conjugate vaccines, which include serotypes commonly associated with macrolide resistance such as serotype 14 in the 7-valent and also serotype 19A in the 13-valent, can then be followed by marked shifts in the prevalence of macrolide-resistant *S. pneumoniae* isolates.^{203–206}

S. pyogenes isolates showing resistance to erythromycin were first reported in the UK in 1955, with resistance rates rising in the 1980s–1990s.^{199–207} However, reduction in resistance rates with reduced macrolide usage has also been found. For instance, Finland likewise experienced a rise in macrolide resistance in the 1980s, which was temporally associated with a rise in macrolide use; however, after nationwide policies were introduced to restrict their use in treating respiratory and soft-tissue infections after 1991, the resistance rate fell in clinical isolates of *S. pyogenes* from 16.5% in 1992 to 8.6% in 1996.²⁰⁸ Similar to *S. pneumoniae*, erythromycin resistance rates are much higher in *S. aureus* isolates that are methicillin resistant compared with those that are methicillin susceptible.¹⁹⁹ The emergence of erythromycin resistance in *S. aureus*, isolated from individual patients on macrolide treatment, has been known since the discovery of the antibiotic.²⁰⁹

As to be expected, increased macrolide resistance has been found in studies evaluating the impact of long-term macrolide use in the setting of chronic lung diseases.^{108–210} A recent metaanalysis of azithromycin use found that, while overall colonisation rates by potential pathogens, such as *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, decreased, the risk of macrolide resistance, macrolide resistance among such pathogens rose 2.7-fold in patients receiving azithromycin when compared with placebo.²¹¹ However, it should also be acknowledged that for any individual patient, the actual clinical impact of the presence of a macrolide-resistant respiratory pathogen, such

as *S. pneumoniae*, at least in the short term, is not clear.²¹² Organisms for which the macrolides are a key pillar of treatment, but in which macrolide resistance can emerge, notably if any macrolide treatment is not accompanied by two or three other active agents in combination, is of particular concern in the use of long-term (ie, months to years) courses of macrolides. Such pathogens include many non-tuberculous mycobacteria (NTM) species, notably the slower growing such as *M. avium* complex. Such organisms may develop resistance by single point mutations, for example, in the 23S rRNA gene. It is well recognised that the long-term success rate of medically treating macrolide-resistant NTM disease is very poor, and much worse than for treating a susceptible organism with a combination including an effective macrolide.²¹³ Current NTM infection should be managed with reference to the BTS Guidelines for the management of non-tuberculous mycobacterial pulmonary disease.²¹⁴

The macrolides, notably azithromycin, also have significant applications outside the respiratory setting—including in regards to some sexually transmitted diseases (STDs), GI infections and zoonoses.^{200,215} One needs to be mindful that their value in such indications is affected by macrolide resistance and also by the rising bacterial resistance rates to other antibiotic classes. Circulating strains of *Neisseria gonorrhoeae* now show resistance to a range of antibiotic classes, to which this organism was initially susceptible. In consequence, the recent standard first-line regimen for suspected gonorrhoea has been ceftriaxone and azithromycin;²¹⁵ however clinical isolates of *N. gonorrhoeae* also resistant to both these agents have now been described.^{200–216–218} The latest UK guidelines, published January 2019, now recommend therapy with ceftriaxone alone as first choice for cases where organism susceptibilities are not known, partly on the grounds of concern of rising macrolide resistance, both among *N. gonorrhoeae* but also in other organisms causing STDs.²¹⁹ Azithromycin is also a recommended first-line therapy for other STDs such as chlamydia (*Chlamydia trachomatis*), chancroid (*Haemophilus ducreyi*) and donovanosis (*Klebsiella granulomatis*).^{200–215} Rising fluoroquinolone resistance rates means that macrolides are the empirical treatment of choice for diarrhoea due to *Campylobacter*; and, in the form of azithromycin, a first-line option for enteric fever acquired in Asia.^{200–217}

Any indications for the macrolide class of antibiotics have been classified, in the main, in the 'Watch' group of antibiotics by WHO; along with six other classes.²²⁰ This categorisation consists of three groups: 'Access', 'Watch' and 'Restrict', the AWaRe classification. The uses of antibiotics in the Watch group should be carefully monitored to ensure they are in accordance with recommended indications. It should be recognised that the available evidence for the potential benefits and harms of long-term macrolide therapy will not capture all the associated risks of increasing antimicrobial resistance. Such studies are not designed to do so, and are too short in timescale and too restricted in patients, and organisms, being studied.

Virtually any antibiotic may be associated with diarrhoea; notably if by precipitating *C. difficile* disease. Although the macrolides appear relatively rare among antibiotic classes as being directly associated with *C. difficile*; clearly if their prior use has led to a pathogen shift, then use of an alternative antibiotic may be required which is more often associated with subsequent *C. difficile* disease.^{198–221}

Antibiotics have been shown to reduce the microbial diversity and alter composition of microbiomes in murine and human studies.^{222–224} Such effects may be greater, and more prolonged, with macrolides than for some other antibiotics classes, such as penicillins.²²² In children at least, receipt of macrolides, and the associated changes in microbial commensal flora, have been linked with other health outcomes, such as asthma and being overweight.²²² This illustrates that if there are identified benefit(s) to offering certain patients with specific chronic respiratory conditions, a macrolide as long-term supportive therapy; the known, and as yet unknown, risks of associated collateral damage should also be carefully considered, by both macrolide prescriber and macrolide consumer.

Good practice points

- ✓ The risks associated with increasing antimicrobial resistance should be discussed with patients prior to starting low dose macrolide therapy. Patients should understand the risk that there may not be an effective antibiotic for them, or someone else, when needed in the future.
- ✓ Prior to initiating low-dose macrolide monotherapy, patients should be asked if they have a history of previous or current NTM

infection or disease. Current NTM infection should be managed with reference to BTS guidance and precludes low-dose macrolide monotherapy. Successfully treated NTM disease should not preclude low-dose macrolide monotherapy.

✓ If there is any clinical suspicion of possible NTM disease, patients should be screened via examination of sputum samples prior to starting therapy. If positive for recognised potential pathogenic species, low-dose macrolide prophylaxis is contraindicated

Contributors All authors drafted and approved the final version of the manuscript. DS and IDR were the lead authors with overall responsibility for the manuscript. funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations cited here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Competing interests BTS Declarations of Interest forms have been completed by all members for each year they were part of the GDG. Details of these forms can be obtained from BTS Head Office.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed. data availability statement Supporting information is available on the BTS website (www.brit-thoracic.org.uk).

ORCID iDs

Simon Paul Hart <http://orcid.org/0000-0003-4606-9559>

Philip J Mitchelmore <http://orcid.org/0000-0002-7850-3068>

References

- Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
- Hill A, L Sullivan A, D Chalmers J, et al. British Thoracic Society guideline for bronchiectasis in adults. *Thorax* 2019;74:1–69.
- NICE. Cystic fibrosis: diagnosis and management. Contract No: NG78. NICE, 2017.
- NICE. Asthma: diagnosis, monitoring and chronic asthma management. Contract No: NG80. NICE, 2017.
- NICE. Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing. Contract No: NG114. NICE, 2018.
- NICE. Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing. NG117[Guideline]. London: NICE, 2018. <https://www.nice.org.uk/guidance/ng117>
- NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Contract No: NG115. London: NICE, 2018.
- Global Initiative for Chronic Global Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. 2019. Available: www.goldcopd.org
- Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017;50:1602265.
- Heraeth SC, Normansell R, Maiese S, et al. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2018;10:CD009764.
- Hnin K, Nguyen C, Carson-Chahhoud KV, et al. Prolonged antibiotics for noncystic fibrosis bronchiectasis in children and adults. *Cochrane Database Syst Rev* 2015;209.
- Normansell R, Sayer B, Waterson S, et al. Antibiotics for exacerbations of asthma. *Cochrane Database Syst Rev* 2018;6:CD002741.
- Kelly C, Chalmers JD, Crossingham I, et al. Macrolide antibiotics for bronchiectasis. *Cochrane Database Syst Rev* 2018;3:CD012406.
- Kew KM, Undela K, Kotorski L, et al. Macrolides for chronic asthma. *Cochrane Database Syst Rev* 2015:CD002997.
- Global Initiative for Asthma. GINA report 2018, global strategy for asthma management and prevention, 2018. Available: <https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf> [Accessed 20 May 2019].
- Hansen MP, Scott AM, McCullough A, et al. Adverse events in people taking macrolide antibiotics versus placebo for any indication. *Cochrane Database Syst Rev* 2019;1:CD011825.
- Itkin IH, Menzel ML. The use of macrolide antibiotic substances in the treatment of asthma. *J Allergy* 1970;45:146–62.
- Zeiger RS, Schatz M, Sperling W, et al. Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma. *J Allergy Clin Immunol* 1980;66:438–46.
- Homma H, Yamakawa A, Tanimoto S, et al. Diffuse panbronchiolitis. A disease of the transitional zone of the lung. *Chest* 1983;83:63–9.
- Kudo S, Uetake T, Hagiwara K, et al. [Clinical effects of low-dose long-term erythromycin chemotherapy on diffuse panbronchiolitis]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1987;25:632–42.
- Koyama H, Geddes DM. Erythromycin and diffuse panbronchiolitis. *Thorax* 1997;52:915–8.
- Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010;23:590–615.
- Altanbulug I, de Graaff CS, van der Werf TS, et al. Immunomodulatory effects of macrolide antibiotics—part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* 2011;81:75–87.
- Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med* 2013;1:262–74.
- BTS/SIGN. British guideline on the management of asthma. BTS/SIGN, 2016.
- Black PN, Scicchitano R, Jenkins CR, et al. Serological evidence of infection with *Chlamydia pneumoniae* is related to the severity of asthma. *Eur Respir J* 2000;15:254–9.
- Gotfried MH, Jung R, Messick CR, et al. Effects of six-week clarithromycin therapy in corticosteroid-dependent asthma: a randomized, double-blind, placebo-controlled pilot study. *Curr Ther Res Clin Exp* 2004;65:1–12.
- Juniper EF, Guyatt GH, Epstein RS, et al. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76–83.
- Black PN, Blasi F, Jenkins CR, et al. Trial of roxithromycin in subjects with asthma and serological evidence of infection with *Chlamydia pneumoniae*. *Am J Respir Crit Care Med* 2001;164:536–41.
- Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013;68:322–9.
- Cameron EJ, Chaudhuri R, Mair F, et al. Randomised controlled trial of azithromycin in smokers with asthma. *Eur Respir J* 2013;42:1412–5.
- Hahn DL, Grasmick M, Hetzel S, et al. Azithromycin for bronchial asthma in adults: an effectiveness trial. *J Am Board Fam Med* 2012;25:442–59.
- Hahn DL, Plane MB, Mahdi OS, et al. Secondary outcomes of a pilot randomized trial of azithromycin treatment for asthma. *PLoS Clin Trials* 2006;1:e11.
- Simpson JL, Powell H, Boyle MJ, et al. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008;177:48–55.
- Sutherland ER, King TS, Ictovic N, et al. A trial of clarithromycin for the treatment of suboptimally controlled asthma. *J Allergy Clin Immunol* 2010;126:747–53.
- Tong X, Guo T, Liu S, et al. Macrolide antibiotics for treatment of asthma in adults: a meta-analysis of 18 randomized controlled clinical studies. *Pulm Pharmacol Ther* 2015;31:99–108.
- Amayasu H, Yoshida S, Ebana S, et al. Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. *Ann Allergy Asthma Immunol* 2000;84:594–8.
- Coeman M, van Durme V, Batters F, et al. Neomacrolides in the treatment of patients with severe asthma and/or bronchiectasis: a retrospective observational study. *Thorax* 2011;66:877–86.
- Evans DJ, Cullinan P, Geddes DM, et al. Troleandomycin as an oral corticosteroid steroid sparing agent in stable asthma. *Cochrane Database Syst Rev* 2001:CD002987.
- Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:659–68.
- Reiter J, Demirel N, Mendy A, et al. Macrolides for the long-term management of asthma—a meta-analysis of randomized clinical trials. *Allergy* 2013;68:1040–9.
- Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
- Nelson HS, Hamilos DL, Corsello PR, et al. A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. *Am Rev Respir Dis* 1993;147:398–404.
- Kamada AK, Hill MR, Iklé DN, et al. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma. *J Allergy Clin Immunol* 1993;91:873–82.
- Bail RD, Hill MR, Brenner M, et al. Effect of low-dose troleandomycin on glucocorticoid pharmacokinetics and airway hyperresponsiveness in severely asthmatic children. *Ann Allergy* 1990;65:37–45.
- Shoji T, Yoshida S, Sakamoto H, et al. Anti-inflammatory effect of roxithromycin in patients with aspirin-intolerant asthma. *Clin Exp Allergy* 1999;29:950–6.
- Wang T, Pei FY, Song XP, et al. Clinical impacts of low-dose azithromycin on lung function and fraction of exhaled nitric oxide: concentration in bronchial asthma. *Med Innovation China* 2014;1:122–4.
- Kostadima E, Tsiodras S, Alexopoulos EI, et al. Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004;23:714–7.
- Lopes Dos Santos Santiago G, Brusselle G, Dauwe K, et al. Influence of chronic azithromycin treatment on the composition of the oropharyngeal microbial community in patients with severe asthma. *BMC Microbiol* 2017;17:109.
- Anwar GA, McDonnell MJ, Worthy SA, et al. Phenotyping adults with non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respir Med* 2013;107:1001–7.
- Lonni S, Chalmers JD, Goeminne PC, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann Am Thorac Soc* 2015;12:1764–70.
- Pasteur MC, Helliwell SM, Houghton SJ, et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000;162:1277–84.
- Quint JK, Millett ERC, Joshi M, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016;47:186–93.
- Shoemark A, Ozerovitch I, Wilson R. Aetiology in adult patients with bronchiectasis. *Respir Med* 2007;101:1163–70.
- Goeminne PC, Scheers H, Decraene A, et al. Risk factors for morbidity and death in non-cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients. *Respir Res* 2012;13:21.
- Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017;50:1700629.
- Fouka E, Lamprianidou E, Arvanitidis K, et al. Low-dose clarithromycin therapy modulates Th17 response in non-cystic fibrosis bronchiectasis patients. *Lung* 2014;192:849–55.
- Liu J, Zhong X, He Z, et al. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. *Mediators Inflamm* 2014;2014:1–14.
- Burr LD, Rogers GB, Chen AC-H, et al. Macrolide treatment inhibits *Pseudomonas aeruginosa* quorum sensing in non-cystic fibrosis bronchiectasis. An analysis from the bronchiectasis and low-dose erythromycin study trial. *Ann Am Thorac Soc* 2016;13:1697–703.
- Davies G, Wilson R. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. *Thorax* 2004;59:540–1.
- Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:660–7.
- Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013;309:1251–9.
- Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013;309:1260–7.
- Hill AT, Welham S, Reid K, et al. British Thoracic Society national bronchiectasis audit 2010 and 2011. *Thorax* 2012;67:928–30.
- Anwar GA, Bourke SC, Afolabi G, et al. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. *Respir Med* 2008;102:1494–6.
- Diego AD, Milara J, Martinez-Morañón E, et al. Effects of long-term azithromycin therapy on airway oxidative stress markers in non-cystic fibrosis bronchiectasis. *Respirology* 2013;18:1056–62.
- Cymbala AA, Edmonds LC, Bauer MA, et al. The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. *Treat Respir Med* 2005;4:117–22.
- Tsang KW, Ho PI, Chan KN, et al. A pilot study of low-dose erythromycin in bronchiectasis. *Eur Respir J* 1999;13:361–4.
- Fan L-C, Lu H-W, Wei P, et al. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. *BMC Infect Dis* 2015;15:160.
- Wu Q, Shen W, Cheng H, et al. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *Respirology* 2014;19:321–9.
- Zhuo G-Y, He Q, Xiang-Lian L, et al. Prolonged treatment with macrolides in adult patients with non-cystic fibrosis bronchiectasis: meta-analysis of randomized controlled trials. *Pulm Pharmacol Ther* 2014;29:80–8. [Erratum appears in *Pulm Pharmacol Ther*. 2014 Oct;29(10):90. PMID: 24752188].
- Chalmers JD, Boersma W, Loneragan M, et al. Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. *Lancet Respir Med* 2019;7:845–54.
- Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017;49:1700051.
- Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity index: An international derivation and validation study. *Am J Respir Crit Care Med* 2014;189:576–85.
- Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC clinical research collaboration. *Eur Respir J* 2017;48:632–47.
- Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117:398S–401.
- Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;67:957–63.
- Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–46.
- Di Stefano A, Caramori G, Gennemi I, et al. T helper type 17-related cytokine expression is increased in the bronchial mucosa of stable chronic obstructive pulmonary disease patients. *Clin Exp Immunol* 2009;157:316–24.
- Sethi S, Murphy TE. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:2355–65.
- Blasi F, Mantero M, Aliberti S. Antibiotics as immunomodulatory agents in COPD. *Curr Opin Pharmacol* 2012;12:293–9.
- Wedzicha JA, Miravittles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017;49:1600791.
- Uzun S, Djamin RS, Klyutmans AJW, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014;2:361–8.
- Simpson JL, Powell H, Baines KJ, et al. The effect of azithromycin in adults with stable neutrophilic COPD: a double blind randomised, placebo controlled trial. *PLoS One* 2014;9:e105609.
- Sethi S, Jones PW, Theron MS, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010;11:10.
- Myrdal LH, Pedersen C, Vestbo J, et al. A randomized, placebo-controlled 3 years study of prophylactic azithromycin in 575 patients with chronic obstructive pulmonary disease (COPD) [Abstract]. European Respiratory Society Annual Congress; September 18–22, Barcelona, Spain, 2010:5580.
- Shafuddin E, Mills GD, Holmes MD, et al. A double-blind, randomised, placebo-controlled study of roxithromycin and doxycycline combination, roxithromycin alone, or matching placebo for 12 weeks in adults with frequent exacerbations of chronic obstructive pulmonary disease. *J Negat Results Biomed* 2015;14:15.
- Pomares X, Montón C, Espasa M, et al. Long-term azithromycin therapy in patients with severe COPD and repeated exacerbations. *Int J Chron Obstruct Pulmon Dis* 2011;6:449–56.
- Yamaya M, Azuma A, Takizawa H, et al. Macrolide effects on the prevention of COPD exacerbations. *Eur Respir J* 2012;40:485–94.
- Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019;53:1900164.
- Weatherall M, Marsh S, Shirlcliffe P, et al. Quality of life measured by the St George's respiratory questionnaire and spirometry. *Eur Respir J* 2009;33:1025–30.
- Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991;85 Suppl B:25–31. discussion 3–7.
- Albert RK, Connell J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;365:689–98.
- Berkhof FF, Hertog NE, Uil SM, et al. Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. *Respir Res* 2013;14:125.
- Jones PW. St. George's respiratory questionnaire: MCID. *COPD* 2005;2:75–9.
- Banerjee D, Khair OA, Honeybourne D. The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD. *Respir Med* 2005;99:208–15.
- He Z-Y, Ou L-M, Zhang J-Q, et al. Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration* 2010;80:445–52.
- Blasi F, Bonardi D, Aliberti S, et al. Long-term azithromycin use in patients with chronic obstructive pulmonary disease and tracheostomy. *Pulm Pharmacol Ther* 2010;23:200–7.
- Roversi S, Corbetta L, Cini E. GOLD 2017 recommendations for COPD patients: toward a more personalized approach. *COPD Research and Practice* 2017;3:5.
- Ni W, Shao X, Cai X, et al. Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. *PLoS One* 2015;10:e0121257.
- Seemungal TAR, Wilkinson TMA, Hurst JR, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008;178:1139–47.
- Suzuki T, Yanai M, Yamaya M, et al. Erythromycin and common cold in COPD. *Chest* 2001;120:730–3.
- Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med* 2014;189:1503–8.
- Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645–8.
- Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011;365:1184–92.
- Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med* 2011;184:1015–21.
- European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease, 2012. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf

- 108 Taylor SP, Sellers E, Taylor BT. Azithromycin for the prevention of COPD exacerbations: the good, bad, and ugly. *Am J Med* 2015;128:1362.e1–6.
- 109 Jain R, Danziger LH. The macrolide antibiotics: a pharmacokinetic and pharmacodynamic overview. *Curr Pharm Des* 2004;10:3045–53.
- 110 Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881–90.
- 111 Lu ZK, Yuan J, Li M, et al. Cardiac risks associated with antibiotics: azithromycin and levofloxacin. *Expert Opin Drug Saf* 2015;14:295–303.
- 112 Almalki ZS, Guo JJ. Cardiovascular events and safety outcomes associated with azithromycin therapy: a meta-analysis of randomised controlled trials. *Am Health Drug Benefits* 2014;7:318–28.
- 113 Blasi F, Damato S, Cosentini R, et al. Chlamydia pneumoniae and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002;57:672–6.
- 114 Berenson CS, Garlapp MA, Grove LJ, et al. Impaired phagocytosis of nontypeable *Haemophilus influenzae* by human alveolar macrophages in chronic obstructive pulmonary disease. *J Infect Dis* 2006;194:1375–84.
- 115 Look DC, Chin CL, Manzel LJ, et al. Modulation of airway inflammation by *Haemophilus influenzae* isolates associated with chronic obstructive pulmonary disease exacerbation. *Proc Am Thorac Soc* 2006;3:482–3.
- 116 Sethi S, Wrona C, Grant JBB, et al. Strain-specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;169:448–53.
- 117 Wu L, Skinner SJ, Lambie N, et al. Immunohistochemical staining for Chlamydia pneumoniae is increased in lung tissue from subjects with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:1148–51.
- 118 Brill SE, Law M, El-Emir E, et al. Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial. *Thorax* 2015;70:930–8.
- 119 Seemungal TAR, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD—a review of potential interventions. *Int J Chron Obstruct Pulmon Dis* 2009;4:203–23.
- 120 Schmidt SAJ, Johansen MB, Olsen M, et al. The impact of exacerbation frequency on mortality following acute exacerbations of COPD: a registry-based cohort study. *BMJ Open* 2014;4:e006720.
- 121 Barker AF, Bergeron A, Rom WN, et al. Obliterative bronchiolitis. *N Engl J Med* 2014;370:1820–8.
- 122 Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 1993;12:713–6.
- 123 Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002;21:297–310. 124 Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J* 2014;44:1479–503.
- 125 Vos R, Vanuaenderde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. *Eur Respir J* 2013;37:164–72.
- 126 Corris PA, Ryan VA, Small T, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. *Thorax* 2015;70:442–50.
- 127 Rutten D, Verleden SE, Vandermeulen E, et al. Prophylactic azithromycin therapy after lung transplantation: post hoc analysis of a randomized controlled trial. *Am J Transplant* 2016;16:254–61.
- 128 Vanuaenderde BM, Meys I, Vos R, et al. A dichotomy in bronchiolitis obliterans syndrome after lung transplantation revealed by azithromycin therapy. *Eur Respir J* 2008;32:832–42.
- 129 Khalid M, Al Saghir A, Saleemi S, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J* 2005;25:490–3.
- 130 Norman BC, Jacobson DA, Williams KM, et al. Fluticasone, azithromycin and montelukast therapy in reducing corticosteroid exposure in bronchiolitis obliterans syndrome after allogeneic hematopoietic SCT: a case series of eight patients. *Bone Marrow Transplant* 2011;46:1369–73.
- 131 Jo K-W, Yoon S, Song JW, et al. The efficacy of prophylactic azithromycin on bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Int J Hematol* 2015;102:357–63.
- 132 Williams KM, Cheng G-S, Pusic I, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2016;22:710–6.
- 133 Lam DCL, Lam B, Wong MKY, et al. Effects of azithromycin in bronchiolitis obliterans syndrome after hematopoietic SCT—a randomized double-blind placebo-controlled study. *Bone Marrow Transplant* 2011;46:1551–6.
- 134 Wolff D, Hildebrandt GC. Bronchiolitis obliterans: pleading for a pragmatic approach. *Biol Blood Marrow Transplant* 2016;22:591–3.
- 135 Mann JM, Sha KK, Kline G, et al. World Trade Center dyspnea: bronchiolitis obliterans with functional improvement: a case report. *Am J Ind Med* 2005;48:225–9.
- 136 Shaw M, Collins BF, Ho LA, et al. Rheumatoid arthritis-associated lung disease. *Eur Respir Rev* 2015;24:1–16.
- 137 Ford AC, Forman D, Moayyedi P, et al. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006;61:975–9.
- 138 Song W-J, Chang Y-S, Faruqi S, et al. Defining chronic cough: a systematic review of the epidemiological literature. *Allergy Asthma Immunol Res* 2016;8:146–55.
- 139 Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001–02. *Vital Health Stat* 13 2006;1–66.
- 140 French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. *Arch Intern Med* 1998;158:1657–61.
- 141 Smith JA, Woodcock A, Cough C. Chronic cough. *N Engl J Med* 2016;375:1544–51.
- 142 Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007;175:312–5.
- 143 Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583–9.
- 144 Jayakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope* 2006;116:2108–12.
- 145 Yousaf N, Matos S, Birring SS, et al. Factors affecting cough frequency in a mixed population. *Thorax* 2009;64(Suppl IV):A151.
- 146 Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchitis and cystic fibrosis. *J Antimicrob Chemother* 2004;54:21–8.
- 147 Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. *Thorax* 2010;65:1107–10.
- 148 Hodgson D, Anderson J, Reynolds C, et al. The effects of azithromycin in treatment-resistant cough: a randomized, double-blind, placebo-controlled trial. *Chest* 2016;149:1052–60.
- 149 Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;63(Suppl 5):v1–58.
- 150 Cottin V, Cordier J-F. Cryptogenic organizing pneumonia. *Semin Respir Crit Care Med* 2012;23:462–75.
- 151 Chang WJ, Lee EJ, Lee SY, et al. Successful salvage treatment of steroid-refractory bronchiolar COP with low-dose macrolides. *Pathol Int* 2012;62:144–8.
- 152 Ding Q-L, Lv D, Wang B-J, et al. Macrolide therapy in cryptogenic organizing pneumonia: a case report and literature review. *Exp Ther Med* 2015;9:829–34.
- 153 Hotta M. Neutrophil chemotactic activity in cryptogenic organizing pneumonia and the response to erythromycin. *Kurume Med J* 1996;43:207–17.
- 154 Ichikawa Y, Ninomiya H, Katsuki M, et al. Low-dose/long-term erythromycin for treatment of bronchiolitis obliterans organizing pneumonia (BOOP). *Kurume Med J* 1993;40:65–7.
- 155 Kastelik JA, Greenstone M, McGivern DV, et al. Cryptogenic organising pneumonia. *Eur Respir J* 2006;28:1291.
- 156 Oh JH, Oh DJ, Koo S-M, et al. Different responses to clarithromycin in patients with cryptogenic organizing pneumonia. *Tuberc Respir Dis* 2015;78:401–7.
- 157 Pathak V, Kuhn JM, Durham C, et al. Macrolide use leads to clinical and radiological improvement in patients with cryptogenic organizing pneumonia. *Ann Am Thorac Soc* 2014;1:187–91.
- 158 Radzikowska E, Rozy A, Jagus P, et al. Clarithromycin decreases IL-6 concentration in serum and BAL fluid in patients with cryptogenic organizing pneumonia. *Adv Clin Exp Med* 2016;25:871–8.
- 159 Radzikowska E, Wiatr E, Gawryluk D, et al. [Organizing pneumonia—clarithromycin treatment]. *Pneumonol Alergol Pol* 2008;76:334–9.
- 160 Stover DE, Mangino D. Macrolides: a treatment alternative for bronchiolitis obliterans organizing pneumonia? *Chest* 2005;128:3611–7.
- 161 Vaz AP, Morais A, Melo N, et al. [Azithromycin as an adjuvant therapy in cryptogenic organizing pneumonia]. *Rev Port Pneumol* 2011;17:186–9.
- 162 D'Elia T. The effectiveness of low-dose azithromycin in relapsing cryptogenic organizing pneumonia: a case report and a review of the literature. *Clin Pulm Med* 2016;23:179–83.
- 163 Azuma A, Kudoh S. Diffuse panbronchiolitis in East Asia. *Respirology* 2006;11:249–61.
- 164 Yamakawa A, Saiki S, Tamura S, et al. Problems in chronic obstructive bronchial diseases, with special reference to diffuse panbronchiolitis. *Naika* 1969;23:442–51.
- 165 Poletti V, Patelli M, Poletti G, et al. Diffuse panbronchiolitis observed in an Italian male. *Sarcoidosis* 1992;9:67–9.
- 166 Fitzgerald JE, King TE, Lynch DA, et al. Diffuse panbronchiolitis in the United States. *Am J Respir Crit Care Med* 1996;154:497–503.
- 167 Lin X, Lu J, Yang M, et al. Macrolides for diffuse panbronchiolitis. *Cochrane Database Syst Rev* 2015;1:CD007716.
- 168 Kudoh S, Azuma A, Yamamoto M, et al. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998;157:1829–32.
- 169 Kondo Y, Torii K, Itoh Z, et al. Erythromycin and its derivatives with motilin-like biological activities inhibit the specific binding of 125I-motilin to duodenal muscle. *Biochem Biophys Res Commun* 1988;150:877–82.
- 170 Broad J, Sanger GJ. The antibiotic azithromycin is a motilin receptor agonist in human stomach: comparison with erythromycin. *Br J Pharmacol* 2013;168:1859–67.
- 171 Tomomasa T, Kuroume T, Arai H, et al. Erythromycin induces migrating motor complex in human gastrointestinal tract. *Dig Dis Sci* 1986;31:157–61.
- 172 Bortolotti M, Brunelli F, Sarti P, et al. Effects of oral clarithromycin and amoxycillin on interdigestive gastrointestinal motility of patients with functional dyspepsia and *Helicobacter pylori* gastritis. *Aliment Pharmacol Ther* 1998;12:1021–5.
- 173 Sifrim D, Matsu H, Janssens J, et al. Comparison of the effects of midecamycin acetate and azithromycin on gastrointestinal motility in man. *Drugs Exp Clin Res* 1994;20:121–6.
- 174 Moshiree B, McDonald R, Hou W, et al. Comparison of the effect of azithromycin versus erythromycin on antroduodenal pressure profiles of patients with chronic functional gastrointestinal pain and gastroparesis. *Dig Dis Sci* 2010;55:675–83.
- 175 Chini P, Toskes PU, Waseem S, et al. Effect of azithromycin on small bowel motility in patients with gastrointestinal dysmotility. *Scand J Gastroenterol* 2012;47:422–7.
- 176 Tzavaras G, Xynos E, Chrysos E, et al. The effect of intravenous erythromycin on esophageal motility in healthy subjects. *Am J Surg* 1996;171:316–9.
- 177 Pennathur A, Tran A, Cioppi M, et al. Erythromycin strengthens the defective lower esophageal sphincter in patients with gastroesophageal reflux disease. *Am J Surg* 1994;167:169–73. discussion 72–3.
- 178 Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut* 1992;33:397–401.
- 179 Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med* 1990;322:1028–31.
- 180 Stacher G, Peeters TL, Bergmann H, et al. Erythromycin effects on gastric emptying, antral motility and plasma motilin and pancreatic polypeptide concentrations in anorexia nervosa. *Gut* 1993;34:166–72.
- 181 Longo WE, Vernava AM. Prokinetic agents for lower gastrointestinal motility disorders. *Dis Colon Rectum* 1993;36:696–708.
- 182 Röhm KD, Bold J, Piper SN. Motility disorders in the ICU: recent therapeutic options and clinical practice. *Curr Opin Clin Nutr Metab* 2009;12:161–7.
- 183 Carter BL, Woodhead JC, Cole KJ, et al. Gastrointestinal side effects with erythromycin preparations. *Drug Intell Clin Pharm* 1987;21:734–8.
- 184 van Noord C, Eigelshelm M, Stricker BHC. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol* 2010;71:16–23.
- 185 Volberg WA, Koci BJ, Su W, et al. Blockade of human cardiac potassium channel human ether-a-go-go-related gene (hERG) by macrolide antibiotics. *J Pharmacol Exp Ther* 2002;302:320–7.
- 186 Swanström H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. *N Engl J Med* 2013;368:1704–12.
- 187 Mosholder AD, Mathew J, Alexander JJ, et al. Cardiovascular risks with azithromycin and other antibacterial drugs. *N Engl J Med* 2013;368:1665–8.
- 188 Shaffer D, Singer S, Korvick J, et al. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration adverse event reporting system. *Clin Infect Dis* 2002;35:197–200.
- 189 Albert RK, Schuller JL. COPD Clinical Research Network. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014;189:1173–80.
- 190 Ikeda AK, Prince AA, Chen JX, et al. Macrolide-associated sensorineural hearing loss: a systematic review. *Laryngoscope* 2018;128:228–36.
- 191 Wallace MR, Miller LK, Nguyen MT, et al. Ototoxicity with azithromycin. *Lancet* 1994;343:241.
- 192 Tseng AL, Dolovich L, Salit IE. Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1997;24:76–7.
- 193 Brown BA, Griffith DE, Girard W, et al. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997;24:958–64.
- 194 Moseley RH. Macrolide antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In: Kaplowitz N, DeLeve LD, eds. *Drug-induced liver disease*. Amsterdam: Elsevier, 2013: 466–7.
- 195 Sundaram V, Björnsson ES. Drug-induced cholestasis. *Hepatol Commun* 2017;1:726–35.
- 196 HM Government. Contained and controlled: the UK's 20-year vision for antimicrobial resistance. Emergency Preparedness and Health Protection Policy Directorate, 2019.
- 197 World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2017–2018. World Health Organization, 2018.
- 198 Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis* 2004;38(Suppl 4):S341–5.
- 199 Sivapalasingam S, Steigbigel NH. Macrolides, clindamycin and ketolides. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas and Bennett's principle and practice of infectious diseases*. 8th edn. Philadelphia: Elsevier Saunders, 2015: 358–76.
- 200 Gordon C. Azithromycin. In: Grayson M, ed. *Kucers' The use of antibiotics*. 7th edn. Boca Raton: CRC Press, 2018: 1122–49.
- 201 Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. *Antimicrob Agents Chemother* 1991;35:1273–6.
- 202 Leclercq R, Courvalin P. Resistance to macrolides and related antibiotics in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2006;46:2727–34.
- 203 Schroeder MR, Stephens DS. Macrolide resistance in *Streptococcus pneumoniae*. *Front Cell Infect Microbiol* 2016;6:98.
- 204 Bergman M, Huikko S, Huovinen P, et al. Macrolide and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2006;50:3646–50.
- 205 Farrell DJ, File TM, Jenkins SG. Prevalence and antibacterial susceptibility of mef(A)-positive macrolide-resistant *Streptococcus pneumoniae* over 4 years (2000 to 2004) of the PROTEKT US Study. *J Clin Microbiol* 2007;45:290–3.
- 206 Imöhl M, Reinert RR, van der Linden M. Antibiotic susceptibility rates of invasive pneumococci before and after the introduction of pneumococcal conjugate vaccination in Germany. *Int J Med Microbiol* 2015;305:776–83.
- 207 Lowbury EJ, Hurst L. The sensitivity of staphylococci and other wound bacteria to erythromycin, oleandomycin, and spiramycin. *J Clin Pathol* 1959;12:163–9.
- 208 Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for antimicrobial resistance. *N Engl J Med* 1997;337:441–6.
- 209 Haight TH, Finland M. Laboratory and clinical studies on erythromycin. *N Engl J Med* 1952;247:227–32.
- 210 Hare KM, Grimwood K, Chang AB, et al. Nasopharyngeal carriage and macrolide resistance in Indigenous children with bronchiectasis randomized to long-term azithromycin or placebo. *Eur J Clin Microbiol Infect Dis* 2015;34:2275–85.
- 211 Li H, Liu D-H, Chen L-L, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother* 2014;58:511–7.
- 212 Cilloniz C, Albert RK, Liapiou A, et al. The effect of macrolide resistance on the presentation and outcome of patients hospitalized for *Streptococcus pneumoniae* pneumonia. *Am J Respir Crit Care Med* 2015;191:1265–72.
- 213 Griffith DE, Aksent T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367–416.
- 214 Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *BMJ Open Respir Res* 2017;4:e000242.
- 215 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Available: <https://www.cdc.gov/std/tg2015/toc.htm>
- 216 Public Health England. UK case of *Neisseria gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad. 12. Health Protection Report, 2018.
- 217 Harris JB RE. Enteric fever and other causes of fever and abdominal symptoms. In: Bennett JE DR, Blaser MJ, eds. *Mandell, Douglas and Bennett's principle and practice of infectious diseases*. 8th edn. Philadelphia: Elsevier Saunders, 2015: 1270–82.
- 218 PHE. Salmonella typhimurium resistant to third-generation cephalosporins isolated in England from a traveller returning from Pakistan. Contract No: Health Protection Report 11. PHE, 2017.
- 219 Fifer H, Saunders J, Soni S, et al. British Association for Sexual Health and HIV national guideline for the management of infection with *Neisseria gonorrhoeae*. BASHH, 2019.
- 220 WHO. The selection and use of essential medicines: report of the 21st WHO Expert Committee on the selection and use of essential medicines. Geneva: WHO, 1977. 221 Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother* 2014;69:881–91.
- 222 Korpela K, Salonen A, Virta LJ, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun* 2016;7:10410.
- 223 Cho I, Yamanishi S, Cox L, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* 2012;488:621–6.
- 224 Jernberg C, Löfmark S, Edlund C, et al. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *Isme J* 2007;1:56–66.
- 225 Donath E, Chaudhry A, Hernandez-Aya LF, et al. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with chronic obstructive pulmonary disease. *Respir Med* 2013;107:1385–92.
- 226 Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2013:CD009764.
- 227 Simoons S, Laekeman G, Decramer M. Preventing COPD exacerbations with macrolides: a review and budget impact analysis. *Respir Med* 2013;107:637–48.
- 228 Yao G-Y, Ma Y-L, Zhang M-Q, et al. Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: a meta-analysis. *Respiration* 2013;86:254–60.
- 229 Lee JS, Park D-A, Hong Y, et al. Systematic review and meta-analysis of prophylactic antibiotics in COPD and/or chronic bronchitis. *Int J Tuberc Lung Dis* 2013;17:153–62.
- 230 Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–22.

O índice de massa corporal e a alteração de peso estão associados a trajetórias da função pulmonar adultas: o estudo prospectivo ECRHS

Gabriela P Peralta,^{1,2,3} Alessandro Marcon,⁴ Anne-Elie Carsin,^{1,2,3,5} Michael J Abramson,⁶ Simone Accordini,⁴ André FS Amaral,⁷ Josep M Antó,^{1,2,3} Gayan Bowatte,^{8,9} Peter Burney,⁷ Angelo Corsico,¹⁰ Pascal Demoly,^{11,12} Shyamali Dharmage,⁸ Bertil Forsberg,¹³ Elaine Fuertes,⁷ Vanessa Garcia-Larsen,¹⁴ Thorarinn Gislason,^{15,16} José-antonio Gullón,¹⁷ Joachim Heinrich,^{8,18,19} Mathias Holm,²⁰ Deborah I Jarvis,^{7,21} Christer Janson,²² Rajni Jogi,²³ Ane Johannessen,^{24,25} Bénédicte Leynaert,^{26,27} Jesús Martínez-Moratalla Rovira,²⁸ Dennis Nowak,^{18,19} Nicole Probst-Hensch,^{29,30} Chantal Raherison,³¹ José-Luis Sánchez-Ramos,³² Torben Sigsgaard,³³ Valérie Siroux,³⁴ Giulia Squillacioti,³⁵ Isabel Urrutia,³⁶ Joost Weyler,³⁷ Jan-Paul Zock,^{1,2,3} Judith Garcia-Aymerich^{1,2,3}

► additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-213880>).

For numbered affiliations see end of article.

Correspondence to

Dr Judith Garcia-Aymerich, ISGlobal, Barcelona 08003, Spain; judith.garcia@isglobal.org

Received 26 July 2019

Revised 19 November 2019

Accepted 16 December 2019

Published Online First

30 January 2020

RESUMO

Contexto Estudos prévios reportaram uma associação entre o aumento de peso e a redução excessiva da função pulmonar em jovens adultos seguidos por períodos curtos. Procurámos estimar trajetórias de função pulmonar durante a idade adulta a partir de perfis de alteração de peso de 20 anos usando dados do estudo *European Community Respiratory Health Survey* (ECRHS) de base populacional.

Métodos Incluímos 3673 participantes recrutados com idades entre 20 e 44 anos com medições repetidas de peso e função pulmonar (capacidade vital forçada (FVC), volume expiratório forçado em 1 seg (FEV₁) em três vagas de estudos (1991-93, 1999-2003, 2010-14) até os participantes terem entre 39 e 67 anos. Classificámos os indivíduos em perfis de alteração de peso de acordo com categorias de índice de massa corporal (IMC) no início do estudo e com a alteração de peso ao longo de 20 anos. Estimámos trajetórias de função pulmonar ao longo do tempo enquanto função dos perfis de alteração de peso recorrendo a equações de estimativa generalizada ponderadas por população.

Resultados Em indivíduos com um IMC normal, excesso de peso e obesidade no início do estudo, os aumentos de peso moderado (0,25-1 kg/ano) e elevado (>1 kg/ano) durante os anos de seguimento foram associados a reduções aceleradas da FVC e do FEV₁. Comparativamente a participantes com um IMC normal no início do estudo e peso estável ($\pm 0,25$ kg/ano), os indivíduos obesos com aumento de peso elevado durante o seguimento apresentaram uma FVC estimada inferior de -1011 ml (95% IC -1259 a -763) aos 65 anos apesar dos níveis de FVC estimados similares aos 25 anos. Os indivíduos obesos no início do estudo que perderam peso (<-0,25 kg/ano) apresentaram uma atenuação das reduções de FVC e do FEV₁. Não encontramos qualquer associação entre perfis de alteração de peso e redução de FEV₁/FVC.

Conclusão O aumento de peso moderado e elevado ao longo de 20 anos esteve associado à redução acelerada da função pulmonar, enquanto a perda de peso esteve relacionada com a sua atenuação. O controlo do aumento de peso é importante para a manutenção de uma boa função pulmonar na vida adulta.

BACKGROUND

Lung function is a significant predictor of future morbidity and mortality in the general population.¹ Maintaining good lung function across adult life is important to prevent chronic respiratory diseases, which nowadays represent a serious public health problem around the world.² There is consistent evidence showing that overweight, obesity and weight gain in adulthood are detrimental to lung function, as described by the forced vital capacity (FVC) and/or forced expiratory volume in 1 s (FEV₁). Previous population-based and occupational cohort studies

Mensagens-chave

What is the key question?

► Is weight change over a 20-year period associated with lung function trajectories in adult life?

What is the bottom line?

► Moderate and high weight gain over a 20-year period was associated with accelerated FVC and FEV₁ decline, while weight loss was related to its attenuation.

Why read on?

► This study, which is based on data collected as part of the multicentre prospective ECRHS study, reinforces the public health message that overweight and obesity have deleterious effects on respiratory health. However, these negative effects can be reversed by weight loss even later in adult life.

have shown that excessive weight gain in adulthood is associated with lower lung function levels and with an increased rate of lung function decline independently of age and smoking status.³⁻⁸ Another longitudinal study in healthy young adults (age range at baseline 18-30 years) showed that lung function was lower both with higher baseline body mass index (BMI) and with increasing BMI over a 10-year period.⁹

Similarly, a population-based study of young adults (mean age at baseline 41 years) analysing the effects of changes in obesity status on lung function found that remaining or becoming obese accelerated lung function decline over an 8-year follow-up, while becoming non-obese was related to its attenuation.¹⁰ All these previous studies have had relatively short follow-up periods (up to 10 years) and most investigated this link only up to 50 years of age. This precludes a more comprehensive understanding of the role of weight change on lung function during adulthood and older life and supports the need for further studies with longer follow-up periods extending into late adult life. Understanding the effects of weight changes on lung function during adult life is of utmost importance given the epidemic levels of overweight and obesity globally.¹¹

The European Community Respiratory Health Survey (ECRHS) is a large multicentre population-based study with available measures of weight, height and lung function at three time points over



© Author(s) (or their employer(s)) 2020. re-use permitted under cc BY. Published by BMJ

Para citar: Peralta GP, Marcon A, Carsin A-E, et al. Thorax 2020;75:313-320.

a 20-year period, as well as detailed information of sociodemographic and lifestyle factors from adults living across Europe and Australia.^{12–14} Under the framework of the Ageing Lungs in European Cohorts (ALEC) consortium (www.alecstudy.org), we aimed to assess the lung function trajectories of adults of the ECRHS study according to different weight change profiles that combined BMI at baseline and weight change over a 20-year period.

METHODS

Study population

The ECRHS started in 1991–1993 (ECRHS I), when over 18000 young adults aged 20–44 years were randomly recruited from available population-based registers (population-based arm), with an oversampling of asthmatics (symptomatic arm). Participants were followed up in 1999–2003 (ECRHS II) and 2010–2014 (ECRHS III) when they were aged 27–57 and 39–67 years, respectively. More details of the study design are available elsewhere.^{12–14} In this analysis we included participants who had weight at ECRHS I and III and lung function and base covariates (sex, age, height and smoking status) at all three surveys (3673 participants from 26 centres in 12 countries) (see online supplementary figure S1).

Ethical approval was obtained from the ethics committees of all participating institutions and all participants provided informed written consent.

Lung function

Lung function was measured by spirometry at ECRHS I, II and III. Centres used different spirometers at ECRHS I and II, but almost all centres used the same spirometer at ECRHS III (see online supplementary table S1). In the three examinations, forced vital capacity (FVC) and forced expiratory volume in 1s (FEV₁), repeatable to 150mL from at least two of a maximum of five correct manoeuvres that met the American Thoracic Society and European Respiratory Society recommendations,¹⁵ were used as the primary outcomes. The FEV₁/FVC ratio was also analysed. In the present analysis, we used lung function measurements collected pre-bronchodilator. We also calculated lung function SD scores (z-scores) using the Global Lung Initiative (GLI) equation references,¹⁶ and used these variables as secondary outcomes.

Weight change profiles

BMI was calculated by dividing measured weight (kg) by measured height (m) squared. We defined categories of BMI at ECRHS I (baseline) as 'underweight' (BMI <20kg/m²), 'normal weight' (20kg/m² ≤ BMI <25 kg/m²), 'overweight' (25kg/m² ≤ BMI <30kg/m²) and 'obese' (BMI ≥30 kg/m²), as in previous ECRHS studies.⁸ We computed weight change during follow-up as the difference between weight measured at ECRHS III and ECRHS I divided by the total time of follow-up (in years) and categorised it into stable weight, weight loss and weight gain.

Since there are no standard references for weight change in adults, we used similar weight change categories as in a recent longitudinal long-term population-based study¹⁷: 'weight loss' (<−0.25 kg/year), 'stable weight' (±0.25kg/year), 'moderate weight gain' (>0.25 to ≤1 kg/year) and 'high weight gain' (>1 kg/year). We combined baseline BMI categories with weight change categories to classify participants in weight change profiles. This combined variable was used as the main exposure variable in the analysis.

Other relevant variables

Sociodemographic and other health data were collected using questionnaires. These included sex, age, age completed fulltime education (<17 years; 17–20 years; >20 years), smoking status (never smoker; ex-smoker; current smoker), secondhand smoke exposure (yes; no) and asthma (yes; no). Current asthma was defined as having reported physician-diagnosed asthma and at least one of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/ at rest/at night-time), asthma attacks, use of inhaled/oral medicines for breathing problems (in the last 12 months), or current use of inhalers, aerosols or tablets for asthma.

Leisure-time vigorous physical activity was assessed at ECRHS II by asking participants how often and for how many hours per week

they usually exercised so much that they got out of breath or sweaty. Participants were categorised as being active if they exercised with a frequency of two or more times a week and with a duration of about 1 hour a week or more, and non-active otherwise.¹⁸ Finally, at ECRHS II participants reported if they presented any of the following long-term limiting illnesses: hypertension, heart disease, diabetes, cancer or stroke.

Statistical analysis

We used population-averaged generalised estimating equations (GEE) to estimate lung function trajectories from age 20 to 67 years (the full age range of the study sample) as a function of weight change profiles. Prior to stratifying models by weight change profiles, we tested the interaction between age, BMI at baseline and weight change, and we found that it was statistically significant for all lung function parameters (p value <0.01 for all models). All GEE models had the individuals as the clustering factor (to account for repeated lung function measurements at ECRHS I, II and III) and an unstructured within-cluster correlation.

GEE models had FVC, FEV₁ or FEV₁/FVC as the outcome variables. Interaction terms between age (or age squared) and weight change profiles were entered to allow for different trajectories of lung function with ageing across weight change profiles. We entered sex as a fixed covariate and height, age, age squared, smoking status,

Table 1 Characteristics of the study sample*

	ECRHS I	ECRHS II	ECRHS III
Characteristics	N (%) or mean (SD)	N (%) or mean (SD)	N (%) or mean (SD)
Symptomatic study arm	544 (14.8)	-	-
Women	1956 (53.3)	-	-
Age in years	34.3 (7.1)	43.0 (7.0)	54.3 (7.1)
Height in cm	170.6 (9.4)	170.3 (9.4)	169.4 (9.5)
Weight in kg	69.5 (13.5)	74.0 (15.1)	77.9 (16.1)
BMI			
Continuous, in kg/m ²	23.8 (3.7)	25.4 (4.3)	27.1 (4.9)
Underweight	453 (12.3)	222 (6.1)	119 (3.2)
Normal weight	2097 (57.1)	1676 (45.8)	1224 (33.3)
Overweight	892 (24.3)	1298 (35.5)	1481 (40.3)
Obese	231 (6.3)	461 (12.6)	849 (23.1)
Smoking status			
Non-smoker	1651 (45.0)	1576 (42.9)	1518 (41.3)
Ex-smoker	818 (22.3)	1119 (30.5)	1500 (40.8)
Current smoker	1204 (32.8)	978 (26.6)	655 (17.8)
Secondhand smoke exposure, yes	1939 (52.9)	1321 (36.1)	680 (18.6)
Current asthma, yes†	378 (10.5)	491 (13.8)	570 (16.2)
Age completed full-time education			
<17 years	675 (21.5)	-	-
17–20 years	1205 (38.4)	-	-
>20 years	1256 (40.1)	-	-
Physical activity. Active status‡	-	1363 (52.2)	-
Any long-term limiting illness, yes§	-	405 (17.1)	-
Lung function			
FVC (mL)	4516 (988)	4354 (980)	3964 (948)
FEV ₁ (mL)	3702 (798)	3485 (790)	3006 (753)
FEV ₁ /FVC (%)	82.3 (6.9)	80.3 (6.5)	75.8 (6.5)
Lung function (z-scores)¶			
FVC z-score	0.01 (0.95)	0.02 (1.00)	-0.08 (0.94)
FEV ₁ z-score	-0.01 (1.06)	-0.03 (1.08)	-0.34 (1.04)
FEV ₁ /FVC z-score	-0.06 (1.03)	-0.10 (1.00)	-0.48 (0.89)

*Some variables had missing values. Number of missing values for ECRHS I: 10 in secondhand smoke exposure, 78 in current asthma, and 537 in age completed full-time education. Number of missing values for ECRHS II: 18 in secondhand smoke exposure, 118 in current asthma, 1062 in physical activity and 1300 in any long-term limiting illness. Number of missing values for ECRHS III: 14 in secondhand smoke exposure and 163 in current asthma.

†Current asthma was defined as having reported physician-diagnosed asthma and at least one of the following: asthma-like symptoms (wheeze, nocturnal chest tightness, attacks of breathlessness after activity/at rest/at night-time), asthma attacks, use of inhaled/oral medicines for breathing problems (in the last 12 months), or current use of inhalers, aerosols or tablets for asthma.

‡Individuals were categorised as being active if they exercised with a frequency of two or more times a week and with a duration of about 1 hour a week or more.

§The following illnesses were considered: hypertension, heart disease, diabetes, cancer or stroke.

¶Lung function z-scores were derived using Global Lung Initiative 2012 equations.

BMI, body mass index; FEV₁, volume expired in the first second; FVC, forced vital capacity.

Table 2 Descriptive statistics of weight change profile

Weight change profiles*		n (%)	Weight eCRhs I (kg) Median (P ₂₅ ; P ₇₅)	Weight eCRhs III (kg) Median (P ₂₅ ; P ₇₅)	Weight change during follow-up (kg/year) Median (P ₂₅ ; P ₇₅)
Weight change profiles*	Weight loss	2 (0.1)†	55.5 (54; 57)	48.5 (45; 52)	−0.3 (−0.4; −0.3)
	Stable weight	167 (4.6)	53 (50; 56)	55 (51; 59)	0.1 (0; 0.2)
	Moderate weight gain	259 (7.1)	53 (50; 58)	65.3 (60; 70.4)	0.5 (0.4; 0.7)
	High weight gain	25 (0.7)†	52 (50; 57)	78 (74; 85)	1.2 (1.1; 1.5)
Normal BMI	Weight loss	38 (1)	63.5 (60; 74)	55 (52; 65)	−0.4 (−0.4; −0.3)
	Stable weight	715 (19.5)	64 (59; 72)	65.8 (60; 74)	0.1 (0.0; 0.2)
	Moderate weight gain	1164 (31.7)	65 (60; 72)	76 (70; 84)	0.5 (0.4; 0.7)
	High weight gain	180 (4.9)	66 (60; 72)	92.4 (86; 98)	1.2 (1.1; 1.4)
Overweight	Weight loss	52 (1.4)	80 (76; 87)	55 (52; 65)	−0.4 (−0.6; −0.3)
	Stable weight	291 (7.9)	79 (73; 85)	65.8 (60; 74)	0.1 (−0.1; 0.2)
	Moderate weight gain	454 (12.4)	80 (73; 86)	76 (70; 84)	0.5 (0.4; 0.7)
	High weight gain	95 (2.6)	79 (70; 85)	92.4 (86; 98)	1.2 (1.1; 1.5)
Obese	Weight loss	46 (1.3)	95 (87; 105)	85 (72; 93)	−0.6 (−0.9; −0.4)
	Stable weight	65 (1.8)	90 (85; 100)	92 (85; 101)	0.1 (−0.1; 0.1)
	Moderate weight gain	85 (2.3)	93 (87; 103)	105 (97.1; 114)	0.5 (0.4; 0.7)
	High weight gain	35 (1)	95 (85; 109)	125 (112; 135)	1.3 (1.1; 1.8)
Overall		3673 (100)	68 (59; 78)	76 (66; 87.3)	76 (66; 87.3)

*Weight change profiles were defined combining BMI at baseline and weight change during follow-up. BMI categories at baseline: underweight: BMI <20 kg/m²; normal weight: 20 kg/m² ≤ BMI <25 kg/m²; overweight: 25 kg/m² ≤ BMI <30 kg/m²; obese: BMI ≥30 kg/m². Weight change was computed as the difference between weight measured at ECRHS III and ECRHS I divided by the total duration follow-up (in years). Weight change categories: weight loss: <−0.25 kg/year; stable: within ±0.25 kg/year; moderate weight gain: 0.25–1 kg/year; high weight gain: >1 kg/year.

†Not analysed further because of small sample size.

current asthma and spirometer type as time-specific covariates. We also included an interaction term between smoking status and age (to account for a faster decline over time in smokers). We centred continuous variables at the mean (over the data from the three examinations) before modelling. Adjusted lung function over age was calculated by setting continuous and categorical variables equal to the mean and proportion, respectively (calculated over the study sample). In a secondary analysis we repeated the models using lung function z-scores instead of absolute lung function values.

To assess whether estimated lung function trajectories differed by sex we tested for sex interactions (by including an interaction term between sex and weight change profiles) and we stratified final models by sex. We performed several sensitivity analyses to assess the robustness of the estimated lung function trajectories to various assumptions regarding confounding, change of spirometry devices or weight change categorisation (see online supplementary file).

All analyses were conducted following a complete case approach in Stata/SE 14.0 (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics of the study sample

Compared with those not included in the present analysis (n=12909), individuals who were included were slightly older, less likely to be current smokers, be exposed to secondhand smoke and had higher educational levels at ECRHS I, but they did not differ in terms of weight, BMI and lung function (see online supplementary table S2).

Table 1 shows the main characteristics of the study sample (n=3673). Mean (SD) age of the study sample was 34.3 (7.1) years at baseline and 54.3 (7.1) years at the last follow-up. Approximately half of the study sample were women (53.3%) and 40% had completed full-time education when they were 20 years of age or older.

At baseline, 12% of the sample was underweight, 57% normal weight, 24% overweight and 6% obese. During follow-up almost 4% of the sample lost weight, 34% had stable weight, 53% had a moderate weight gain and 9% had a high weight gain. Table 2 shows descriptive statistics of the 16 weight change profiles identified. Almost 20% of the sample was classified in the weight change profile with baseline normal BMI and stable weight during follow-up.

Out of the groups who lost weight during follow-up, obese participants at baseline were those who lost more weight over time (median −0.6 kg/year, P₂₅–P₇₅ −0.9 to −0.4), while among those who experienced a moderate increase in weight, median weight gain was the same in the different categories of baseline BMI. Among those with high weight gain during follow-up, overweight and obese participants at baseline were those who gained more weight. Underweight participants who lost weight or had a high weight gain represented less than 1% of the study sample and therefore were excluded from further analyses.

Associations between weight change profiles and lung function trajectories

To facilitate interpretation of results, the estimated trajectories of lung function by weight change profiles are presented separately for

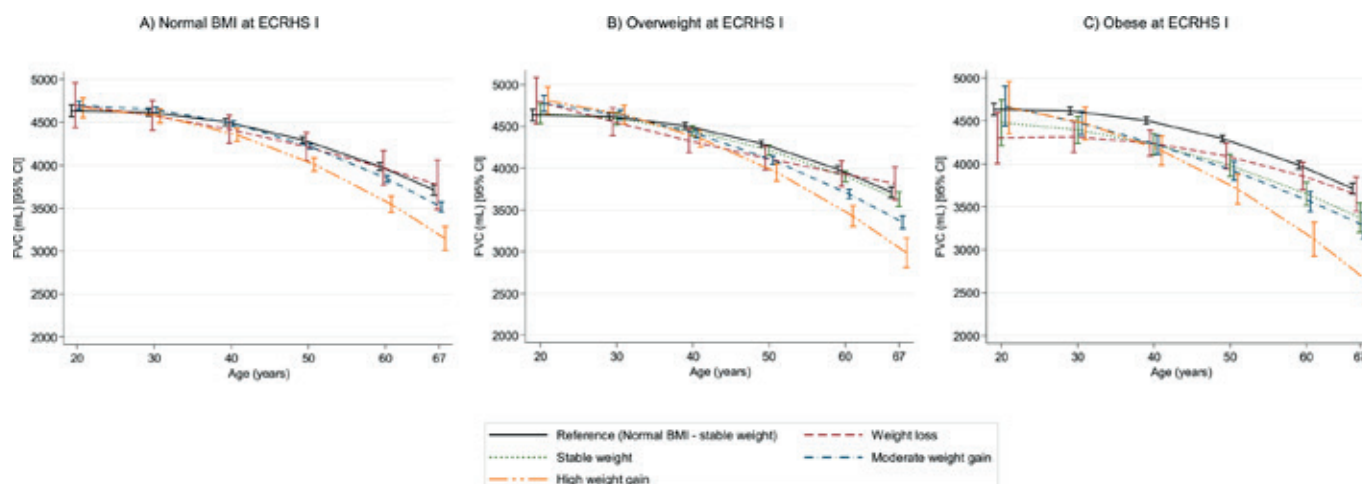


Figure 1 Estimated trajectories of FVC (in mL) decline by weight change profiles. The figure shows estimated FVC values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FVC, forced vital capacity.

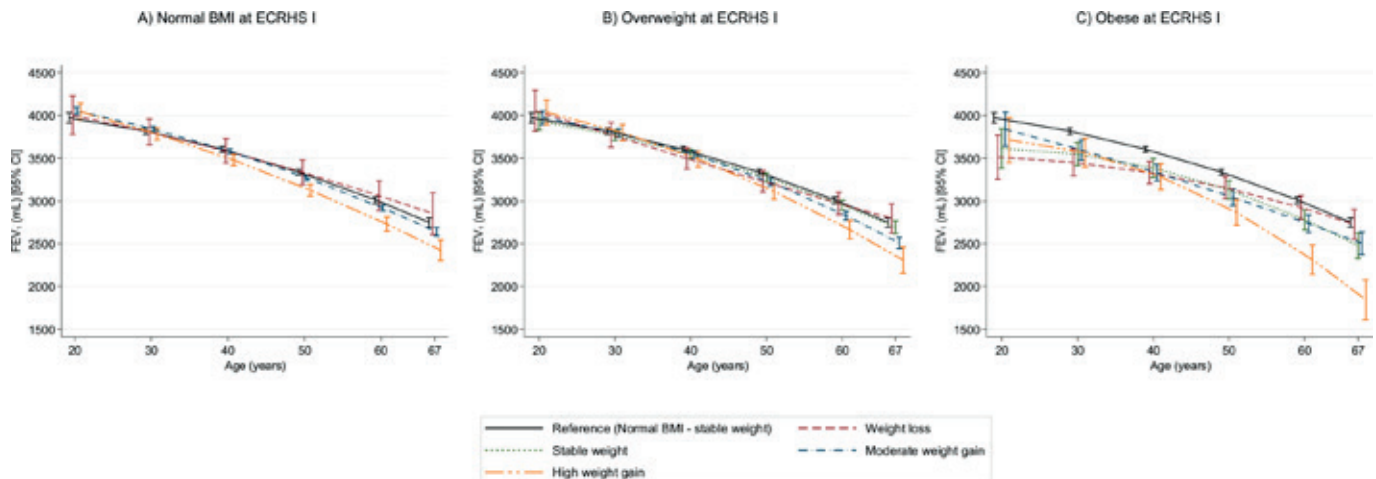


Figure 2 Estimated trajectories of FEV₁ (mL) decline by weight change profiles. The figure shows estimated FEV₁ values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FEV₁, forced expiratory volume in 1 s.

normal BMI, overweight and obese categories at baseline (figures 1–3). Among adults with baseline normal BMI, overweight and obesity, those with moderate and high weight gain during follow-up exhibited significantly steeper FVC decline than those with stable weight (Panels A, B and C in figure 1).

Estimated differences in FVC at 25 and 65 years by weight change profiles (see online supplementary table S3) show that, in comparison with participants with baseline normal BMI and stable weight, baseline overweight and obese participants with high weight gain had lower estimated FVC at 65 years (–677 mL (95% CI –841 to –512); $p < 0.001$ and –1.011 mL (–1.259 to –763); $p < 0.001$, respectively) despite similar estimated FVC levels at age 25 (see online supplementary table S3).

In contrast to weight gain, obese (but not overweight or normal BMI) adults at baseline who lost weight during follow-up exhibited an attenuation of FVC decline (panel C in figure 1). We estimated that, at age 25 years, obese participants had lower FVC levels than normal BMI participants. However, obese individuals who lost weight during follow-up were estimated to have not significantly different FVC values at age 65 years than participants with baseline normal BMI and stable weight (see online supplementary table S3).

Supplementary figure S2 shows lung function trajectories for subjects with baseline underweight. In young adulthood, participants with baseline underweight had lower estimated FVC values than baseline normal BMI participants (see online supplementary figure S2). However, baseline underweight participants with stable weight during follow-up were estimated to have very similar FVC

values at age 65 to participants with baseline normal BMI and stable weight. We found very similar results for estimated FEV₁ trajectories (figure 2, online supplementary figure S2 and table S4). We found no evidence that FEV₁/FVC ratio trajectories were different by weight change profiles, except for two groups.

Subjects with baseline underweight who had stable weight or moderate weight gain showed a steeper decline in FEV₁/FVC ratio than participants with baseline normal BMI and stable weight during follow-up (figure 3, online supplementary figure S2 and table S5).

Secondary analysis using lung function z-scores instead of absolute lung function showed similar results to the main analysis for all lung function parameters (see online supplementary figure S3). Stratification by sex showed that FVC and FEV₁ decline was steeper in men who gained weight than in their female counterparts, particularly in the obese category (see online supplementary figure S4 and S5), but there was no difference with regard to the FEV₁/FVC ratio (see online supplementary figure S6). All sensitivity analyses showed very similar results (see online supplementary figure S7–S12). However, the lung function differences between the reference category and some overweight/obese weight change profiles were attenuated when the analyses were restricted to participants who reported to be non-smokers at all examinations and when additionally adjusting for physical activity, educational level and any longterm limiting illness.

DISCUSSION

In this population-based study we found that weight change over a 20-year period was associated with the rate of lung function decline

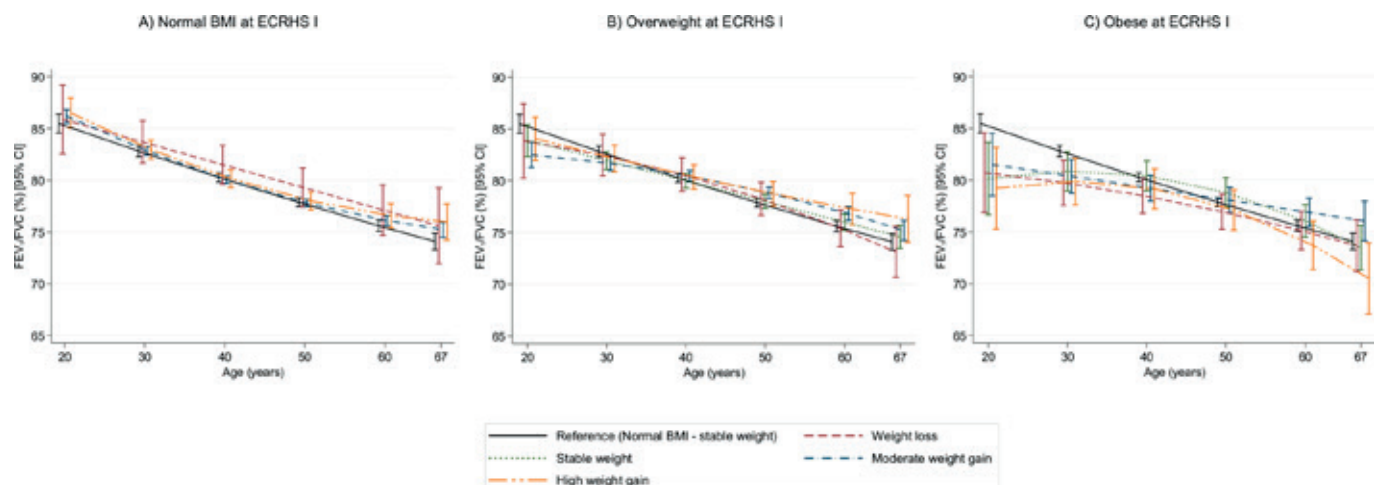


Figure 3 Estimated trajectories of FEV₁/FVC (%) decline by weight change profiles. The figure shows estimated FEV₁/FVC values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

in adulthood. Specifically, we found that: (1) in participants with baseline normal BMI, overweight and obesity in young adulthood, moderate and high weight gain during follow-up were associated with accelerated FVC and FEV₁ decline; (2) in participants with obesity in young adulthood, weight loss during follow-up was associated with attenuated FVC and FEV₁ decline; (3) in underweight participants in young adulthood, stable weight during follow-up was associated with an attenuation of FVC and FEV₁ decline; and (4) we found no evidence of an association between weight change and FEV₁/FVC ratio decline, with the exception of underweight participants with either stable weight or moderate weight gain, both of whom exhibited accelerated FEV₁/FVC ratio decline over follow-up.

Interpretation

Our findings that moderate and high weight gain accelerates FVC and FEV₁ decline and that weight loss attenuates it are consistent with previous research in young adults.^{3–10} This demonstrates how weight changes can affect lung function until late adulthood. Our approach of combining baseline BMI categories with weight change over time let us distinguish the effects of different weight change profiles on lung function throughout adult life. Two potential mechanisms have been proposed to explain the association of weight gain with accelerated lung function decline. First, weight gain can affect lung function through mechanical effects on lungs.

Abdominal and thoracic fat mass are likely to reduce vital capacity by limiting the room for lung expansion during inspiration, in turn leading to expiratory flow limitation.¹⁹ These mechanical effects may also explain the observed sex differences in relation to lung function decline, consistent with previous studies,^{4,8,20} as men tend to accumulate more fat mass in the abdominal area than women.²¹ Second, weight gain can impair lung function by inflammatory processes, as adipose tissue is a source of inflammatory mediators^{22,23} that can damage lung tissue and reduce airway diameter.²⁴ Unfortunately, we did not have measures of chest compliance or markers of systemic inflammation related to obesity, and therefore we could not disentangle the mechanical effects of body mass on lung function from the inflammatory effects.

There are some potential mechanisms that can explain the association between weight loss and attenuation of lung function decline in obese subjects. First, it is possible that weight loss reverses the mechanical effects of overweight/obesity on the respiratory system allowing the recovery of lung function. Second, weight loss may relate to a reduction of inflammatory processes in the lung which in turn can help to attenuate lung function decline related to excessive weight. This hypothesis is supported by previous research showing that lung function decline associated with air pollution, which likely affects lung function via inflammation, could be attenuated with improvement of air quality.²⁵ Third, weight loss may be accompanied by improvement of metabolic alterations related to excess body weight, such as insulin dysregulation, high fasting glucose levels, hyperlipidaemia or systemic hypertension, which are also related to impaired lung function.^{26,27} Fourth, the observed association between weight loss and attenuated lung function decline could be related to confounding by changes in lifestyle (eg, increasing physical activity or changing diet) that can follow awareness of the harmful effects of overweight/obesity. Indeed, quitting smoking and becoming physically active in adulthood has been related to better lung function levels and/or attenuated lung function decline.^{8,18,28,29}

Although we accounted for changes in smoking status during follow-up, levels of physical activity and presence of long-term limiting illness that could be accompanied by metabolic alterations (hypertension, heart disease, diabetes, cancer or stroke) at ECRHS II in sensitivity analyses, we did not have information on physical activity or diet at baseline. Further studies with repeated measures of lifestyle factors and indicators of metabolic dysregulation associated with weight changes are needed to disentangle the mechanisms underlying the association of weight loss and attenuated lung function decline.

We also found that stable weight during follow-up in individuals underweight in young adulthood was associated with attenuated

FVC and FEV₁ decline, while those with baseline underweight and moderate weight gain had a parallel FVC and FEV₁ decline to individuals with baseline normal BMI in late adulthood. These findings contrast with results of a previous longitudinal study showing that increasing BMI in initially thin adults (aged 18–30) was associated with lung function improvement over 10 years.⁹ This inconsistency could be related to differences in the definition of weight gain (ie, the use of BMI gain vs weight change) and to a different baseline age range. The relationship between weight change and lung function has received little attention in healthy underweight individuals, so further research is needed to understand the effects of weight change in underweight individuals and their underlying mechanisms.

In the present analysis we did not observe statistically different FEV₁/FVC ratio trajectories by weight change profiles, except for underweight subjects with either stable weight or moderate weight gain during follow-up, both of whom exhibited a faster FEV₁/FVC decline over follow-up. The observed associations in underweight subjects are in line with findings of one previous study in healthy adults⁹ and allow us to hypothesise that underweight subjects could be more susceptible to the development of airflow limitation with ageing.

Also, the lack of association of weight gain with the FEV₁/FVC ratio in the present analysis is in line with previous studies showing that the FEV₁/FVC ratio is normal in overweight and obese individuals.¹⁹ The lack of association of weight gain with the FEV₁/FVC ratio could be attributed to the fact that both FVC and FEV₁ declines were accelerated with weight gain, which could lead to a null net effect on the ratio of these two measures (as both denominator and numerator were equally affected). This pattern suggests that weight gain is likely to be related to a restrictive pattern characterised by a reduction of lung volumes with no effect on airflow limitation. This hypothesis is supported by previous evidence showing that obesity is more likely to be associated with a restrictive ventilatory pattern than an obstructive one.³⁰

Strengths and limitations

A strength of the current study is the long follow-up (up to 20 years) and the width of age distribution covering early to late adulthood. The population-based nature of the ECRHS and broad geographical representation of participants (26 centres in 12 countries in Europe and Australia) support external validity of our results. Finally, we had lung function measures at three time points, which allowed us to estimate lung function trajectories.

A limitation of this study is the use of total body weight as the main exposure. Although total body weight has been largely used in epidemiological studies as a marker of overweight and obesity, it is limited by its inability to distinguish between fat and muscle mass, which vary with age and sex^{31,32} and could have different effects on lung function, as previously shown in children.³³ Also, we defined weight change categories using only weight measures at baseline and last follow-up to capture 'stable' weight change patterns and facilitate the interpretability of our results. Of note, the correlation between individual weight change per year (taking into account three weight measurements) and the weight change variable used in our analysis was 0.998, which justifies our approach.

However, we recognise that our approach precludes us from determining how long it takes for a change in weight to affect lung function decline. Given the lack of standard references for weight change in adults, we categorised weight change based on a previous longitudinal study,¹⁷ limiting the interpretation of our findings to our definition of 'stable weight' ($\pm 0.25\text{kg/year}$). However, the results were very similar when repeating our analysis using a wider category for 'stable weight' ($\pm 0.50\text{kg/year}$), suggesting that our findings are robust even with a less restrictive definition of 'stable weight'.

Our results may also be affected by selection bias, as participants were more likely to be highly educated and less likely to be current smokers or to be exposed to secondhand smoke than those lost to follow-up. Because these factors have been previously associated with lung function, our associations could be underestimates of the true

associations in the general population. Although we accounted for a wide range of confounders, our results could be affected by potential residual confounding by, for example, dietary intake, which affects both body weight and lung function, as the available data on diet were limited to a small subset of the study sample at ECRHS II and III. Moreover, the spirometers used for lung function assessment were changed in some centres, which could have led to systematic differences inherent in lung function measurement that may differ by age and height.³⁴ However, when we adjusted our analysis for spirometer type and when we replicated the analyses using lung function values corrected for change in spirometer we obtained consistent results. Finally, we used three repeated measures of lung function from a sample aged 20–44 years (mean (SD) age 34.3 (7.1) years) at baseline and 39–67 years (mean (SD) age 54.3 (7.1) years) at the last follow-up to estimate lung function trajectories throughout adulthood. However, few participants were aged around 20 years at baseline and around 67 years at the last follow-up, and in consequence the models had fewer observations at the age ends than between 30 and 60 years where most of the observations were.

CONCLUSION

In conclusion, this prospective population-based study shows that moderate and high weight gain over a 20-year period was associated with accelerated lung function decline in adulthood, while weight loss was related to its attenuation. Our findings, together with the existing literature, reinforce the public health message that overweight and obesity have deleterious effects on health including respiratory health. However, the negative effects of overweight and obesity on lung function can be reversed by weight loss even later in adult life. Therefore, public health policies that promote healthy lifestyles and body weight may be important for maintaining good lung function in adult life.

Author affiliations

- ¹ISGlobal, Barcelona, Spain
- ²Universitat Pompeu Fabra (UPF), Barcelona, Spain
- ³Ciber epidemiologia y salud P6blica (CIBERESP), Barcelona, Spain
- ⁴Unit of epidemiology and Medical statistics, Department of Diagnostics and Public health, University of Verona, Verona, Italy
- ⁵IMIM (hospital del Mar Medical research institute), Barcelona, Spain
- ⁶School of Public health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
- ⁷National heart and lung institute, Imperial college London, London, UK
- ⁸Allergy and lung health Unit, centre for epidemiology and Biostatistics, school of Population & global health, The University of Melbourne, Melbourne, Victoria, Australia
- ⁹National institute of Fundamental studies, Kandy, Sri Lanka
- ¹⁰Division of respiratory Diseases, IRCCS 'San Matteo' hospital Foundation University of Pavia, Pavia, Italy
- ¹¹D6partement de Pneumologie et addictologie, h6pital arnaud de Villeneuve, University hospital of Montpellier, Montpellier, France
- ¹²UMr-s 1136 Inserm, iPlesP, UPMC, sorbonne Universit6s, Paris, France
- ¹³Section of sustainable health, Department of Public health and clinical Medicine, Ume6 University, Ume6, Sweden
- ¹⁴Program in human nutrition, Department of international health, Johns Hopkins Bloomberg school of Public health, Baltimore, Maryland, USA
- ¹⁵Department of sleep, landspitali University hospital Reykjavik, Reykjavik, Iceland
- ¹⁶Medical Faculty University of Iceland, Reykjavik, Iceland
- ¹⁷Department of Pneumology, hospital san agust6n, avil6s, Spain
- ¹⁸Institute and Outpatient clinic for Occupational, social and environmental Medicine, University hospital Munich (LMU), Munich, Germany
- ¹⁹Comprehensive Pneumology center Munich (CPC-M), German center for lung research (DZL), Munich, Germany
- ²⁰Department of Occupational and environmental Medicine, Sahlgrenska University hospital, Gothenburg, Sweden
- ²¹Mrc-Phe centre for environment and health, Imperial college London, London, UK
- ²²Department of Medical sciences, respiratory, allergy and sleep research, Uppsala University, Uppsala, Sweden
- ²³Lung clinic, Tartu University hospital, Tartu, Estonia
- ²⁴Department of global Public health and Primary care, University of Bergen, Bergen, Norway
- ²⁵Department of Occupational Medicine, Haukeland University hospital, Bergen, Norway
- ²⁶Inserm U1168, ViMa (aging and chronic Diseases, epidemiological and Public health approaches), Villejuif, France
- ²⁷UMr-s 1168, Univ Versailles St-Quentin-en-Yvelines, St-Quentin-en-Yvelines, France
- ²⁸Facultad de Medicina de albacete, Universidad de castilla - la Mancha, albacete, Spain
- ²⁹Dwiss Tropical and Public health institute, Basel, Switzerland
- ³⁰Department of Public health, University of Basel, Basel, Switzerland
- ³¹Inserm U897, institute of Public health and epidemiology, Bordeaux University, Bordeaux, France
- ³²Department of nursing, University of huelva, huelva, Spain
- ³³Department of Public health, section for environment Occupation and health, Danish ramazzini centre, Aarhus University, Aarhus, Denmark
- ³⁴Institute for advanced Biosciences, Uga-Inserm U1209-cnrs UMR 5309, Team of environmental epidemiology applied to reproduction and respiratory health, Grenoble, France
- ³⁵Department of Public health and Pediatrics, University of Turin, Turin, Italy
- ³⁶Department of respiratory, galdakao hospital, Galdakao, Spain
- ³⁷Department of epidemiology and social Medicine, University of Antwerp, Antwerp, Belgium

Twitter Gabriela P Peralta @gabriela___p, alessandro Marcon @alemagoo, Vanessa Garcia-Larsen @dietandlungs and Judith Garcia-Aymerich @judithgarciaaym

Contributors GPP, AM, A-ec and Jg-a designed the study. GPP wrote the initial draft and conducted the statistical analyses. Jg-a had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

Funding The present analyses are part of the ageing lungs in European cohorts (alec) study (www.alecstudy.org), which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 633212. The local investigators and funding agencies for the European community respiratory health survey are reported in the online supplement. ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya. Disclaimer The funding sources were not involved in the study design, the collection, analysis and interpretation of data or in the writing of the report and in the decision to submit the article for publication.

Competing interests Jg-a reports personal fees from Esteve, Chiesi and AstraZeneca, outside the submitted work. MJA reports grants from Pfizer, grants from Boehringer-Ingelheim and personal fees from Sanofi, outside the submitted work. PD reports personal fees from Alk, Stallergenes Greer, IQVIA, Chiesi, AstraZeneca, Thermo Fisher Scientific, Menarini, Bausch & Lomb, Mylan, Asit Biotech, Novartis, Sanofi and Regeneron, outside the submitted work. RJ reports grants from Estonian Research Council (Personal research grant no 562) and personal fees from GSK, Boehringer and Novartis, outside the submitted work.

Patient consent for publication not required.

Ethics approval Each participating centre obtained ethical approval from their local ethics committees and followed the rules for ethics and data protection from their country, which were in accordance with the Declaration of Helsinki.

Provenance and peer review not commissioned; externally peer reviewed.

Data availability statement no data are available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Gabriela P Peralta <http://orcid.org/0000-0002-6312-2916>
alessandro Marcon <http://orcid.org/0000-0002-2778-658X>
simone accordini <http://orcid.org/0000-0003-1510-6193>
andr6 Fs amaral <http://orcid.org/0000-0002-0369-9449>
elaine Fuertes <http://orcid.org/0000-0003-0205-9025>
Deborah I Jarvis <http://orcid.org/0000-0002-1753-3896>
christer Janson <http://orcid.org/0000-0001-5093-6980>
Judith Garcia-Aymerich <http://orcid.org/0000-0002-7097-4586>

REFERENCES

- 1 Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007;30:616–22.
- 2 Young RP, Hopkins R. Primary and secondary prevention of chronic obstructive pulmonary disease: where to next? *Am J Respir Crit Care Med* 2014;190:839–40.
- 3 Wang M-L, McCabe L, Petsonk EL, et al. Weight gain and longitudinal changes in lung function in steel workers. *Chest* 1997;111:1526–32.
- 4 Bottai M, Pistelli F, Di Pede F, et al. Longitudinal changes of body mass index, spirometry and diffusion in a general population. *Eur Respir J* 2002;20:665–73.
- 5 Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study of adults. *Int J Obes* 1999;23:979–85.
- 6 Chen Y, Horne SL, Dosman JA. Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study. *Thorax* 1993;48:375–80.
- 7 Chinn DJ, Cotes JE, Reed JW. Longitudinal effects of change in body mass on measurements of ventilatory capacity. *Thorax* 1996;51:699–704.
- 8 Chinn S, Jarvis D, Melotti R, et al. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet* 2005;365:1629–35.
- 9 Thyagarajan B, Jacobs DR, Apostol GG, et al. Longitudinal association of body mass index with lung function: the CARDIA study. *Respir Res* 2008;9:31.
- 10 Pistelli F, Bottai M, Carrozzi I, et al. Changes in obesity status and lung function decline in a general population sample. *Respir Med* 2008;102:674–80.
- 11 The World Health Organization. Obesity and overweight. available: <http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> [accessed 22 Aug 2018].
- 12 Burney PGJ, Luczynska C, Chinn S, et al. The European community respiratory health survey. *Eur Respir J* 1994;7:954–60.
- 13 Jarvis D. European community respiratory health survey II steering committee. The European community respiratory health survey II. *Eur Respir J* 2002;20:1071–9.
- 14 Janson C, Anto J, Burney P, et al. The European community respiratory health survey: what are the main results so far? European community respiratory health survey II. *Eur Respir J* 2001;18:598–611.
- 15 Miller MR, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- 16 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- 17 Park S-Y, Wilkens LR, Maskarinec G, et al. Weight change in older adults and mortality: the Multiethnic cohort study. *Int J Obes* 2018;42:205–12.
- 18 Fuertes E, Carls A-E, Ant6 JM, et al. Leisure-time vigorous physical activity is associated with better lung function: the prospective ECRHS study. *Thorax* 2018;73:376–84.
- 19 Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* 2010;108:206–11.
- 20 Marcon A, Corsico A, Cazzoletti I, et al. Body mass index, weight gain, and other determinants of lung function decline in adult asthma. *J Allergy Clin Immunol* 2009;123:1069–74.
- 21 Harik-Khan R, Wise RA, Fleg JL. The effect of gender on the relationship between body fat distribution and lung function. *J Clin Epidemiol* 2001;54:399–406.
- 22 Ferrante AW. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med* 2007;262:408–14.
- 23 Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr* 2006;83:461S–5.
- 24 Hancox RJ, Poulton R, Greene JM, et al. Systemic inflammation and lung function in young adults. *Thorax* 2007;62:1064–8.
- 25 Schikowski T, Schaffner E, Meier F, et al. Improved air quality and attenuated lung function decline: modification by obesity in the SaPaDia cohort. *Environ Health Perspect* 2013;121:1034–9.
- 26 Baffi CW, Wood L, Winnica D, et al. Metabolic syndrome and the lung. *Chest* 2016;149:1525–34.
- 27 Phelan S, Wadden TA, Berkowitz R, et al. Impact of weight loss on the metabolic syndrome. *Int J Obes* 2007;31:1442–8.
- 28 Garcia-Aymerich J, Lange P, Benet M, et al. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:458–63.
- 29 Willemsse BW, Postma DS, Timens W, et al. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J* 2004;23:464–76.
- 30 Zammit C, Liddicoat H, Moonsie I, et al. Obesity and respiratory diseases. *Am J Clin Hypn* 2011;53:335–43.
- 31 He X, Li Z, Tang X, et al. Age- and sex-related differences in body composition in healthy subjects aged 18 to 82 years. *Medicine* 2018;97:e11152.
- 32 Meeuwse S, Horgan GW, Elia M. The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. *Clin Nutr* 2010;29:560–6.
- 33 Peralta GP, Fuertes E, Granel R, et al. Childhood body composition trajectories and adolescent lung function. findings from the alsPac study. *Am J Respir Crit Care Med* 2019;200:75–83.
- 34 Briddaevaux P-O, Dupuis-Lozeron E, Schindler C, et al. Spirometer replacement and serial lung function measurements in population studies: results from the SaPaDia study. *Am J Epidemiol* 2015;181:752–61.

Defesa da continuidade de CPAP e VNI comunitárias durante a epidemia COVID-19

Jillian G Baker,^{1,2} Milind Sovani²

Dear Editor,

Recent clinical guidelines regarding the use of home non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) during the COVID-19 epidemic have tried to balance the risks of stopping NIV or CPAP against the unknown potential risk of increased aerosol-related transmission to family and carers.^{1,2} We read with interest views put forward by Barker et al³ but feel that wider aspects need consideration, and for NIV and CPAP separately.

NIV use: NIV is primarily used for those with previous, or at risk from, hypercapnic respiratory failure (neuromuscular disorders, chest wall deformity, obesity or underlying lung disease, for example, COPD).

Stopping home NIV risks the return of symptoms (lethargy, headache, dyspnoea and confusion), increased patient and family anxiety and precipitating life-threatening acute hypercapnia, which is likely to result in hospital admission, patient exposure to COVID-19 and other infections, as well as causing increased (and preventable) pressure on ventilator beds. Home NIV patients often have limited mobility or are housebound.

They have been advised to self-isolate and, in our experience, most patients are following the advice. There is therefore a higher risk of a carer to patient transmission. NIV does generate droplets, but using a non-vented mask with a viral filter reduces the spread significantly.⁴ We however recognise that should patient get infected then there is a risk to carers.

¹School of Life Sciences, University of Nottingham, Nottingham, UK

²Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

Correspondence to Professor Jillian G Baker, School of Life Sciences, University of Nottingham, Nottingham NG7 2RD, UK; Jillian.Baker@nottingham.ac.uk

Continuing home NIV, with increased family member care, backed up with remote assistance from specialist carers, is an option. When direct carer input cannot be avoided, simple measures, for example, hand washing and opening windows and doors before a visit to reduce airborne viral load (a single change of room air reduces viral load by 63%, five changes to less than 1%,⁵) and personal protective equipment will be required.

For patients in care facilities or requiring hospital admission, a side room and pre-emptive change of mask and circuit with a viral filter in combination with precautions listed above should minimise risk. CPAP use: CPAP is primarily used for those with obstructive sleep apnoea (OSA). While CPAP treatment improves symptoms (sleepiness, headaches, concentration, memory and mood) it is rarely life-preserving. However, stopping home CPAP may cause a deterioration in physical and mental health, in addition to social distancing and home isolation. Increased sleepiness will affect driving and safety critical jobs and work productivity may fall. The return of snoring may reduce family members' sleep, affecting household temperaments and compounding frustration from being confined to the home.

Stopping CPAP for the entire epidemic duration cannot be recommended, especially for key workers, those with safety critical jobs and those with increased workload during the pandemic. If a CPAP user develops symptoms (or has asymptomatic proven COVID-19) then self-isolation and stopping CPAP for 2 weeks might be sensible. To minimise any in-hospital transmission, we are asking patients not to bring home CPAPs, masks or equipment into hospital (assuming contamination) and are not treating straightforward OSA with CPAP in hospital during the epidemic.

Patients with decompensated obesity hypoventilation or COPD/OSA overlap will be provided with a non-vented mask, viral filter and vented circuit in a side room with a hospital CPAP machine.

Thus, while we fully accept there is an unknown, potentially increased, risk of viral transmission for other household members and carers, should the NIV-user or CPAP user be COVID-19 positive, we believe that blanket advice to withhold home NIV and CPAP for all users, for what may be a substantial period (maybe 12 weeks or even longer), will cause significant, and measurable, patient harm.

Contributors JGB and MS are the sole authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JGB provides molecular pharmacology advice for CuraSen Therapeutics. MS has received speaking fees from Chiesi, StraZeneca and Radiometer, received assistance from ResMed towards attending ERS, received funding from RESMED, Breas and Philips Respironics towards organising a Sleep and Ventilation course and received a £45,000 Research Grant and four Transcutaneous carbon dioxide monitors (TCM5) as well as consumables from Radiometer towards a multicentre study.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.



To cite Baker JG, Sovani M. Thorax 2020;75:368.

Published Online First 9 April 2020



► <http://dx.doi.org/10.1136/thoraxjnl-2020-214890>
Thorax 2020;75:368.
doi:10.1136/thoraxjnl-2020-214913

REFERENCES

- Guidance regarding coronavirus (COVID-19) and obstructive sleep apnoea (OSA): for people who routinely use continuous positive airway pressure (CPAP), their families and health care workers. Available: <https://www.brit-thoracic.org.uk/media/455098/osa-alliance-cpap-covid-19-advice-20-3-20-v10.pdf> [Accessed 20 Mar 2020].
- NHS. Clinical guide for the use of acute non-invasive ventilation in adult patients hospitalised with suspected or confirmed coronavirus during the coronavirus pandemic. Available: <https://www.england.nhs.uk/coronavirus/wpcontent/uploads/sites/52/2020/03/clinical-guide-acute-niv-ventilation-v-1-19-march-2020.pdf>
- Barker J, Oyefeso O, Koeckerling D, et al. COVID-19: community CPAP and NIV should be stopped unless medically necessary to support life. Thorax 2020;75:367.
- Simonds AK, Hanak A, Chatwin M, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess 2010;14:131-72.
- Public Health England. COVID-19: guidance for infection prevention and control in healthcare settings. version 1.0. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872745/Infection_prevention_and_control_guidance_for_pandemic_coronavirus.pdf

COVID-19: A CPAP e a VNI comunitárias devem ser interrompidas exceto se forem medicamente necessárias para suporte de vida

Joseph Barker,¹ Oluwatobiloba Oyefeso,² David Koeckerling,³ Nadeesha Lakmal Mudalige,⁴ Daniel Pan⁵

Dear Editor,

Data from the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) outbreak suggest high viral load at the time of transmission is associated with worse clinical outcomes.¹ Non-invasive ventilation (NIV), including CPAP, is currently listed by the WHO as a high-risk aerosolgenerating procedure putting healthcare workers at risk and necessitates the use of personal protective equipment.^{2,3}

The current UK guidance does not account for high-dose viral transmission risk to family and carers in patients using community NIV and CPAP for treatment of chronic respiratory disease, especially obstructive sleep apnoea.

National Health Service guidance states for patients who remain at home during the coronavirus pandemic to continue with their usual method of ventilation.⁴

The British Thoracic Society guidance for obstructive sleep apnoea advocates patient choice to determine implementation of distancing measures while using

CPAP or stopping CPAP for a short time. It goes on to encourage patients to persist with CPAP when experiencing symptoms of respiratory infection.⁵

Zou and colleagues reported comparable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load detection in nasal and throat swabs of symptomatic and asymptomatic patients, suggesting NIV-induced aerosolisation of nasopharyngeal secretions from asymptomatic patients may pose similar risks for high-dose viral transmission in households.⁶ Aerosolised SARS-CoV-2 is reported to have a half-life of 1.1 hours in air and therefore a period of prolonged isolation may be required following NIV usage.⁷ Universal isolation for NIV and CPAP usage within households may not be practical and individualised consideration should be given to temporary cessation of community ventilation, taking into account the risks of withholding NIV in hypercapnia.⁸

While we agree that data are limited, we believe the risk of high-dose viral transmission of SARS-CoV-2, from community NIV and CPAP users to household members, to be highly plausible and with potentially severe consequence.

In the interests of patients' families and their carers we call for a consensus opinion on clearer instructions for patients and their physicians—how to isolate while using NIV or CPAP at home, safety provisions for household members and risk-benefit analysis of temporary NIV or CPAP cessation.

A response by Baker and Sovani to the views expressed here has also been published in *Thorax*.⁹

Twitter Joseph Barker @jarbark

Contributors All authors contributed equally to manuscript authorship and revision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Barker J, Oyefeso O, Koeckerling D, et al. *Thorax* 2020;75:367.



Published Online First 9 April 2020



► <http://dx.doi.org/10.1136/thoraxjnl-2020-214913>

Thorax 2020;75:367.
doi:10.1136/thoraxjnl-2020-214890

ORCID iD

Joseph Barker <http://orcid.org/0000-0002-5483-9608>

REFERENCES

1. Chu C-M, Poon LLM, Cheng VCC, et al. Initial viral load and the outcomes of SARS. *CMAJ* 2004;171:1349–52.
2. Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.
3. World Health Organization (WHO). Rational use of personal protective equipment (PPE) for coronavirus disease (COVID-19), 2020. Available: https://apps.who.int/iris/bitstream/handle/10665/331498/WHO-2019-nCoV-IPCPE_use-2020.2-eng.pdf
4. NHS. Clinical guide for the use of acute non-invasive ventilation in adult patients hospitalised with suspected or confirmed coronavirus during the coronavirus pandemic, 2020. Available: <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/clinical-guide-acute-niv-ventilation-v1-19-march-2020.pdf> [Accessed 23 Mar 2020].
5. Society BT. Guidance regarding coronavirus (COVID-19) and obstructive sleep apnoea (OSA): for people who routinely use continuous positive airway pressure (CPAP), their families and health care workers, 2020. Available: <https://www.brit-thoracic.org.uk/media/455098/osa-alliance-cpap-covid-19-advice-20-3-20-v10.pdf>
6. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382:1177–9.
7. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020. doi:10.1056/NEJMc2004973. [Epub ahead of print: 17 Mar 2020].
8. Köhlein T, Windisch W, Köhler D, et al. Non-Invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
9. Baker JG, Sovani M. Case for continuing community NIV and CPAP during the COVID-19 epidemic. *Thorax* 2020;75:368

Medjournal

A sua editora de publicações médicas

Já se encontra disponível gratuitamente a edição *online* da publicação *Thorax* com artigos do *Archives of Diseases in Childhood* para os Médicos Portugueses, para poder ter acesso, pedimos o seu registo em www.medjournal.pt

Gestão da bronquiolite grave: impacto das orientações NICE

Benedict Griffiths, Shelley Riphagen, Jon Lillie

South Thames Retrieval Service,
Paediatric Intensive Care Unit,
Evelina London Children's
Hospital, London, UK

Correspondence to

Dr Benedict Griffiths, Paediatric
Intensive Care, Evelina London
Children's Hospital, London SE1
7EH, UK;
bgriffiths@doctors.org.uk

Received 19 March 2018

Revised 29 October 2018

Accepted 7 November 2018

Published Online First

24 November 2018



© Autor(es) (ou o(s) seu(s)
empregador(es)) 2020. Não é
permitida a utilização com fins
comerciais. Consultar direitos e
permissões. Publicado pela BMJ.

RESUMO

Objetivo Compreender o impacto das orientações relativas à bronquiolite do *National Institute for Health and Care Excellence* (NICE) para a gestão de crianças referenciadas para unidades de cuidados intensivos pediátricos (UCIP) com bronquiolite.

Desenho e enquadramento Foram recolhidos dados de todas as crianças referenciadas para um serviço de transporte UCIP regional com diagnóstico clínico de bronquiolite durante o inverno anterior ao do período de consulta NICE (2011-2012) e durante o inverno após a publicação (2015-2016). Foi avaliada a gestão iniciada pelo hospital referenciador.

Resultados Na época 1, foram referenciadas 165 crianças com bronquiolite e, na época 2, foram referenciadas 187 crianças. A utilização de nebulizador aumentou de 28% na época 1 para 53% na época 2. Observaram-se um aumento da utilização de oxigénio por cânula nasal de fluxo elevado e uma redução da utilização da ventilação por pressão positiva contínua. A utilização de antibióticos manteve-se inalterada entre épocas.

Conclusão A utilização de terapêuticas nebulizadas aumentou na gestão da bronquiolite grave apesar da orientação nacional em sentido contrário.

INTRODUÇÃO

Acute viral bronchiolitis is the most common reason for admission to paediatric intensive care units (PICU) in the UK and continues to represent a significant burden on acute admission to paediatric wards. The National Institute for Health and Care Excellence (NICE) published guidelines in June 2015 to support clinicians in the management of children with bronchiolitis.¹ The impact of this effort to standardise therapy has yet to be assessed.

The guideline made several key recommendations pertinent to the management of severe bronchiolitis, including:

1. Avoidance of all nebulised therapies.
2. Consider continuous positive airway pressure (CPAP) in children with bronchiolitis who have impending respiratory failure.
3. Antibiotics are not indicated. We hypothesised that in a severe subgroup of patients referred to PICU, guidelines would have little impact on practice. We investigated the management of children referred to a regional paediatric intensive care retrieval service before and after the introduction of the guideline.

METHOD

The South Thames Retrieval Service (STRS) provides advice and accepts paediatric intensive care referrals for all children who are critically ill from 22 district general hospitals (DGH) in the south of England covering an estimated child population of 2.1 million.

The study was registered with the audit department of Guy's and St Thomas' Foundation Trust. Data were collected for all referrals to STRS with the reported diagnosis of bronchiolitis between 1

What is already known on this topic?

- There is large variation in bronchiolitis management across the UK.
- Bronchiolitis is the most common reason for admission to paediatric intensive care units in the UK.
- NICE guidelines published in 2015 advised avoidance of nebulised therapies, and recommended the use of continuous positive airway pressure in patients with impending respiratory failure.

Mensagens-chave

- Nebulisers are still widely used in the management of children with bronchiolitis and their use increased during the time the NICE guidelines were published.
- High-flow nasal cannula (HFNC) oxygen use has increased between 2012 and 2015.
- Evidence for the use of HFNC in bronchiolitis should be analysed and subsequent guidance be updated.

October and 31 March 2011–2012 (epoch 1) and 2015–2016 (epoch 2). Epoch 1 occurred prior to the NICE consultation period and epoch 2 occurred after publication of the guideline in June 2015. Designated lead paediatric consultants were contacted to inform them of the NICE guideline and that management would be audited.

Inclusion criteria were: all children under 1 year of age presenting with physician-diagnosed acute viral bronchiolitis. Children with known previous wheeze were excluded to avoid any confusion with recurrent viral wheeze. Where children were referred to STRS more than once in the same episode of illness only the initial referral was considered.

Data collection was prospective with cases identified at the time of referral and data extracted and recorded by members of the retrieval service. The STRS database was subsequently screened retrospectively at the end of the study period for any missed referrals using the diagnosis code 'bronchiolitis'. All data collected were double-checked against the original referral form for accuracy by the study authors.

Baseline demographic data, presenting symptom, investigations and local management (including method of respiratory support) were collected. Outcome data were collected for length of PICU stay (LOS), length of invasive ventilation (LOV) episode, final diagnosis and mortality.

Para citar: Griffiths B,
Riphagen S, Lillie J.
Arch Dis Child
2020;105:483–485

Table 1 Demographics; median and IQR for continuous variables

	EPOCH 1 2011–2012 N=132	EPOCH 2 2015–2016 N=153	P Values
Age chronological (days)	52 (30–96)	67 (39–135)	0.02
Age (days, corrected for gestation)	39 (17–79)	46 (12–104)	0.68
Prematurity	26% (n=34)	40% (n=61)	0.01
Weight (kg)	4.2 (3.3–5.5)	4.3 (3.2–6.0)	0.40
Presenting symptom: apnoea	33% (n=43)	34% (n=52)	0.80
Serum sodium (mmol/L)	137 (135–140)	138 (136–140)	0.08
Haemoglobin (g/L)	110 (98–125)	109 (93–121)	0.56

Mann-Whitney U test provides p values. Proportion with apnoea and prematurity shown (χ^2 test). Statistical significance if $p < 0.05$ in bold.

Statistical analysis was performed using STATA V.14.2 software (StataCorp, Texas). Data are expressed as median (IQR) or count (percentage) as appropriate, with between-epoch differences analysed using the t-test (continuous data) and the normal approximation to the binomial test (count data). Logistic regression was used to compare nebuliser use against age across epochs.

RESULTS

Baseline demographics are shown in table 1, the only significant clinical difference was that more babies were born prematurely in the later epoch (40% vs 26%). The apparent increase in chronological age in epoch 2 disappeared after correction for gestation ($p=0.02$ and $p=0.68$, respectively).

Nebulised therapies

Surprisingly, nebuliser usage increased over time with less than one-third in epoch 1 and over a half of patients in epoch 2 receiving a nebulised therapy ($p < 0.001$) (table 2).

The largest increase was in the use of hypertonic saline (HS; 8% vs 29%, $p < 0.001$). There was also a statistically significant increase in the use of 0.9% saline (7% vs 22%, $p < 0.001$).

Nebuliser use increased with age in both groups and patients were twice as likely to be given nebulisers in epoch 2 regardless of age, OR 2.2 (1.5–3, 95% CI) (see figure 1).

Non-invasive ventilation

The use of non-invasive ventilation at the DGH also changed considerably: high-flow nasal cannula oxygen (HFNC) increased significantly from 8% in 2011–2012 to 55% in 2015–2016 ($p < 0.001$). There was a trend towards reduction in CPAP use (44% vs 36%) and increase in the use of bilevel positive airway pressure but neither reached statistical significance.

Antibiotics

The use of antibiotics in this cohort of patients referred to PICU stayed at approximately 70% in both eras.

Table 2 Therapies received expressed as percentage and absolute number of patients

	2011–2012 N=132	2015–2016 N=153	P Values
Nebuliser used (any)	28% (37)	53% (81)	<0.001
0.9% saline	7% (9)	22% (33)	<0.001
Hypertonic saline	8% (10)	29% (44)	<0.001
Ipratropium bromide	18% (24)	27% (42)	0.06
Salbutamol	8% (10)	12% (19)	0.18
Epinephrine	5% (7)	1% (2)	0.05
Intravenous bronchodilator	2% (3)	1% (1)	0.25
Antibiotics administered	67% (94)	71% (108)	0.48
HFNC O2	8% (10)	55% (84)	<0.001
CPAP	44% (59)	36% (55)	0.13
BIPAP (non-invasive)	0%	3% (4)	0.06
Ventilated at referral	18% (24)	12% (18)	0.12

BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula.

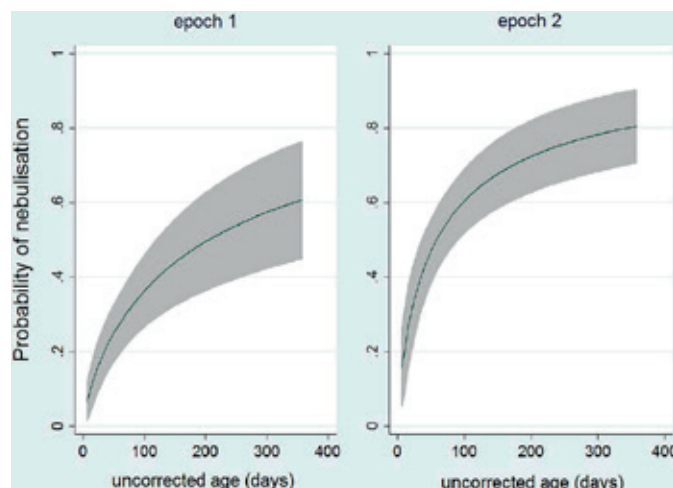


Figure 1 Graphs showing probability of nebuliser use increases with age. Patients were twice as likely to receive nebulisers in the second epoch, OR 2.2 (1.5–3, 95% CI).

Referral outcome

Examining the outcomes for patients referred to the retrieval service: it can be seen those remaining at the DGH on HFNC increased from 2% to 17% ($p < 0.001$) and those retrieved to PICU for invasive ventilation fell from 82% to 68% ($p=0.01$) (see table 3). A similar number of patients stayed at the referring hospital without respiratory support in both groups.

Outcome data were available for >94% of patients in both epochs. There was no significant difference in the LOV on PICU or in the LOS between years. LOV was longer in patients born prematurely with a median LOV of 4.2 days compared with 3.3 days in term babies. Bronchiolitis was the discharge diagnosis in 97% of cases in 2011 and 94% in 2015. In each epoch, one patient died at anaesthetic induction prior to the arrival of STRS.

After retrieval, one patient died in the first epoch with respiratory syncytial virus acute respiratory distress syndrome despite extracorporeal membrane oxygenation. Lung biopsy identified congenital lung disease.

DISCUSSION

The most striking finding of this study was the widespread use of nebulised therapies which has increased significantly over the 4 years since NICE began its consultation. The greatest increase was observed in nebulised HS which has been trialled in bronchiolitis because of its mucolytic properties. NICE acknowledged in their analysis possible evidence of decreased PICU admission based on weak data but cost analysis outweighed any potential benefit suggesting its use. The evidence relating to bronchodilator therapy is clearer with no benefit shown; this therefore represents a clearer failure of translation to practice.

Moreover, patients with previous episodes of wheeze were deliberately excluded so there is no suggestion that any of these infants may have been diagnosed as 'recurrent wheezers'. Perhaps clinicians still suffer the 'frustrated anxiety to do something, anything to relieve the severe dyspnea of bronchiolitis', first discussed by Wright and Beem in 1965.² Yet there is the potential for harm and increased use of nebulisers may prolong LOS.³

There was a dramatic increase in the use of HFNC between years. A smaller proportion of patients required PICU in the later epoch where HFNC and nebuliser use was higher, however no conclusions can be inferred due to methodological limitations. Most importantly, the severity of illness was not measured and referral criteria for contacting STRS include the use of HFNC in some hospitals. HFNC has become a widespread therapy during the NICE consultation period and subsequent guideline publication.⁴ The emerging evidence was therefore not considered and the guidelines make no reference to it.⁵

Table 3 Outcome of patients referred with bronchiolitis and eventual outcome of patients retrieved to PICU

Outcome—all patients referred			
	2011–2012 (132)	2015–2016 (153)	P Values
DGH (no respiratory support)	3% (4)	4% (6)	0.68
DGH (HFNC)	2% (2)	17% (26)	<0.001
DGH (CPAP)	11% (15)	10% (15)	0.67
PICU (NIV)	1% (1)	1% (1)	0.91
PICU (ventilated)	82% (108)	68% (104)	0.01
% Retrieved in network	94% (102)	94% (98)	0.90
Death	2% (2)	1% (1)	0.91
Outcome—patients retrieved to PICU			
	2011–2012 (102)	2015–2016 (98)	P Values
Length of stay (days)	4.7 (3.6–6.4)	5.2 (4.0–7.4)	0.42
Length of ventilation (days)	3.5 (2.5–5.0)	4.0 (2.7–5.3)	0.28
Bronchiolitis was PICU D/C diagnosis	98% (100)	95% (93)	0.30

CPAP, continuous positive airway pressure; D/C, discharge; DGH, district general hospital; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; PICU, paediatric intensive care unit.

NICE does not recommend the use of antibiotics in patients presenting with bronchiolitis, however, up to 40% of bronchiolitis in PICU may have bacterial coinfection so it is reasonable that those referred to PICU be treated empirically with antibiotics.⁶ This study collected data during the first winter following publication of the NICE guideline. A potential limitation is that it took place too soon after guideline introduction. In the USA, there was a significant drop in use of bronchodilators and steroids reported after national guidelines were published by the

American Paediatric Association but this effect was measured 5 years after introduction.⁷

Reasons for non-compliance with guidelines have been examined in the literature; information overload, human nature and length of guidance have all been cited as reasons for clinicians to deviate from them.⁸ With so many complex barriers to changing clinician behaviour cited, careful strategies for education and engagement will be required to ensure children with severe bronchiolitis receive an evidence-based approach to their management.

Acknowledgements Shane Tibby for guidance and statistical analysis; Akash Deep (King's College PICU) and Martin Gray (St George's PICU) for providing outcome data.

Contributors JL and SR designed the study. JL and BG collected and analysed the data. All three authors were involved in writing the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 National Institute for Health and Care Excellence. Bronchiolitis: diagnosis and management of bronchiolitis in children. Clinical Guideline NG9, 2015.
- 2 Wright FH, BEEM MO. Diagnosis and treatment: Management of acute viral bronchiolitis in infancy. *Pediatrics* 1965;35:334–7.
- 3 Skjerven HO, Hunderi JO, Brüggmann-Pieper SK, et al. Racemic adrenaline and inhalation strategies in acute bronchiolitis. *N Engl J Med* 2013;368:2286–93.
- 4 Milési C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med* 2017;43:209–16.
- 5 Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018;378:1121–31.
- 6 Kneyber MC, Blussé van Oud-Alblas H, van Vliet M, et al. Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. *Intensive Care Med* 2005;31:680–5.
- 7 Parikh K, Hall M, Teach SJ. Bronchiolitis management before and after the AAP guidelines. *Pediatrics* 2014;133:e1–e7.
- 8 Carthey J, Walker S, Deelchand V, et al. Breaking the rules: understanding noncompliance with policies and guidelines. *BMJ* 2011;343:d5283.

**RESEARCH TO
PUBLICATION**

Develop your
research skills

And learn how to write
papers that get published

Research to Publication is an eLearning programme for early career academics in healthcare research brought to you by BMJ.

The full programme will offer a comprehensive set of 8 courses, comprising 52 self-study modules that will allow you to choose what to study, and to do so at your own pace.

Focused on clinical and public health research, the programme draws on the expertise of The BMJ's research editors and UCSF's academics to guide you through the entire process from designing a study to seeing it published.



Enrol today to start learning rtop.bmj.com

UCSF
University of California
San Francisco

BMJ

Implementação do rastreio orientado de cancro do pulmão em população de risco elevado no âmbito da prática clínica no NHS através de tomografia computadorizada de dose reduzida

Helen Grover,^{1,2} Thomas Ross,¹ Elizabeth Fuller^{2,3}

¹Research and Development, South Tyneside and Sunderland NHS Foundation Trust, South Shields, UK

²Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK

³Respiratory Medicine, South Tyneside District General Hospital, South Shields, UK

Correspondence to

Dr Helen Grover, Research and Development, South Tyneside and Sunderland NHS Foundation Trust, South Shields NE34 0PL, UK; helen.grover1@nhs.net

Received 12 November 2019

Revised 20 December 2019

Accepted 6 January 2020

Published Online First

3 March 2020



© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

RESUMO

Reportamos um programa de rastreio orientado de cancro do pulmão em âmbito de cuidados primários que utilizou TC de dose reduzida (TCDR) em South Tyneside e Sunderland. Foram identificados sempre fumadores com ≥ 10 anos-maço entre os 55 e 74 anos na revisão anual de DPOC. 925 indivíduos compareceram para a realização de TCDR. 2% ($n=19/925$) apresentaram diagnóstico de cancro do pulmão. 66,7% ($n=14/21$) apresentaram doença em fase precoce e 78,9% ($n=15/19$) receberam uma proposta de tratamento com intenção de curar. 79,3% dos indivíduos que compareceram para a realização de TCDR foram classificados nos quintis de carência mais baixos. Esta abordagem tem sido implementada com sucesso na prática clínica de rotina no NHS. É eficaz em termos de melhorias de fase da doença e envolve indivíduos em áreas carenciadas.

INTRODUCTION

Public Health England data show that the North East and Cumbria have the second highest age- and sex-standardised incidence and mortality of lung cancer.¹ Lung cancer and chronic respiratory disease contribute greatly to the life expectancy inequality gap, only behind heart disease in both sexes. People in the most deprived areas are more than twice as likely to die prematurely (age <75) from cancer.² They are also less likely to participate in screening for lung cancer.³

The NHS Atlas of Variation in Healthcare suggested that, to reduce premature mortality from cancer, commissioners need to support cancer prevention initiatives including cancer screening programmes.⁴

Airflow obstruction has been identified as an independent risk factor for the development of lung cancer,⁵ and the addition of emphysema to screening criteria has improved lung cancer detection rates.⁶ The National COPD Audit Programme (2016) suggested that 89.3% of patients in the North of England attended primary care review within the preceding 12 months.⁷

This has the potential to be a suitable group to target screening. South Tyneside Clinical Commissioning Group (CCG) and South Tyneside NHS Foundation Trust therefore commissioned a new targeted screening programme for individuals attending annual COPD review in general practice offering low-dose CT (LDCT).

METHODS

The eligibility criteria and participant journey is described in figure 1. Individuals were ineligible if they were housebound, had a CT chest in

the last 12 months or had symptoms needing a 2-week wait referral.

A feasibility pilot project was done and subsequently rolled out across South Tyneside and Sunderland CCGs. Training and written guidelines were provided. Eligible individuals were identified by practice nurses.

All LDCTs are performed out of hours (unless individuals request otherwise) at a cost of £94 per LDCT, including a report. LDCTs take place at static site scanners at South Tyneside District Hospital. Follow-up CTs for nodule surveillance are covered as part of the block contract for the radiology department. A LDCT report is given by a thoracic radiologist who is the lung cancer multidisciplinary team lead. Historical imaging is available to compare. A positive scan is a suspicious lesion or a growing nodule.

Volumetry is used for nodule measurement. Nodule follow-up is as per British Thoracic Society guidelines,⁸ and interval scan details are included in the report. A false positive was any individual seen in the one-stop clinic who was not diagnosed with cancer.

RESULTS

From February 2017 to October 2019, 925 individuals attended for LDCT. Data regarding those patients eligible for LDCT but declining the invitation are unavailable. 68.9% had a negative LDCT ($n=637/925$). 5% of individuals had a positive LDCT ($n=46/925$) and were seen in the one-stop clinic. The false positive rate was 2.4% ($n=22/925$) of all individuals who had a LDCT.

One died suddenly prior to review and four are still pending interval imaging for ground glass nodules. Investigations performed for participants who were not diagnosed with lung cancer included staging CT scan ($n=19$), positron-emission tomography (PET)-CT ($n=4$), bronchoscopy ($n=8$), CT-guided biopsy ($n=1$) and mediastinal biopsy for anterior mediastinal mass ($n=2$). One patient had surgery for benign disease. There were no complications from surgery or investigations. Lung cancer prevalence was 2% ($n=19/925$), with 21 cancers overall as two patients had two lung cancers detected. Participant and cancer characteristics are detailed in table 1.

Pathological types included adenocarcinoma and squamous cell, with six tumours having a clinical diagnosis without histological confirmation. Stage of cancers was as follows: stage I 61.9% ($n=13/21$), stage II 4.8% ($n=1/21$), stage III 28.6% ($n=6/21$) and stage IV 4.8% ($n=1/21$). The surgical resection rate was 15.8% ($n=3/19$). 36.8% had stereotactic ablative radiotherapy (SABR; $n=7/19$), with one awaiting SABR refer-

Para citar: Grover H, Ross T, Fuller E. Thorax 2020;75:348–350.

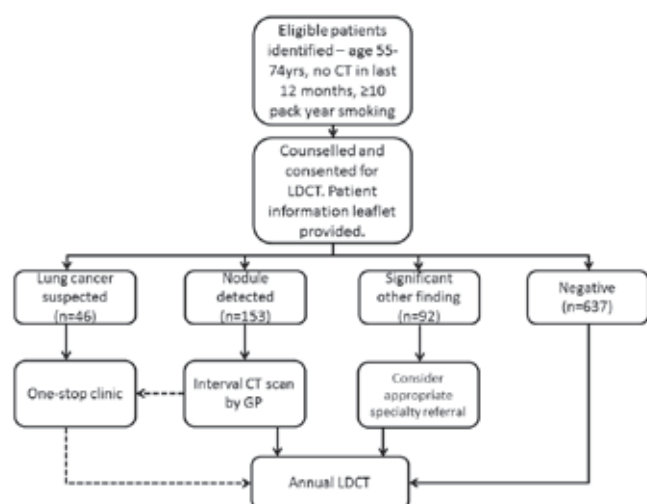


Figure 1 Participant journey through the lung cancer targeted screening programme. LDCT, low-dose CT.

ral, and 21.1% (n=4/19) had concurrent chemoradiotherapy. A curative intent treatment was offered in 78.9% (n=15/19). In all treated patients there were no deaths within 90 days. 16.5% of LDCTs had a nodule or inflammatory change (n=153/925). Of these, 7.2% were referred to the respiratory team for ongoing surveillance (n=11). GPs requested and acted on follow-up CT scans appropriately in 89.4% (n=118/132). 9.6% (n=89/925) of reports suggested another respiratory disease (ie, interstitial lung disease or bronchiectasis). Two breast cancers were diagnosed and one pancreatic lesion considered benign.

DISCUSSION

We report a novel NHS-commissioned service targeting individuals attending annual COPD review. The prevalence of lung cancer is similar to UK Lung Cancer Screening; however, it is lower compared with targeted Lung Health Check (LHC). The overall shift was towards lower stage disease (see figure 2),

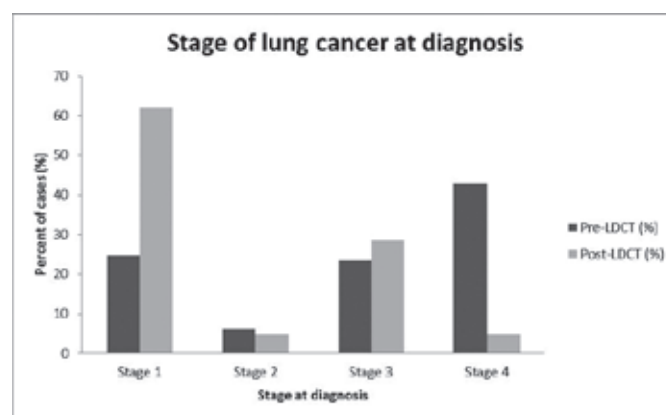


Figure 2 Stage of lung cancer at diagnosis: National Lung Cancer Audit 2016 South Tyneside compared with low-dose CT (LDCT) programme.

although there is bias comparing this selected group with an unselected group as the historical control. The rate of surgical resection is lower and this may reflect the fact that individuals had lower lung function and higher rates of comorbidities (see table 1). There was a high use of SABR, and this is an appropriate radical treatment for these individuals. The mortality rate for those screened in the first 12 months was only 4.6%, hopefully mitigating overdiagnosis in this otherwise comorbid group. GPs have engaged well with nodule follow-up.

A driving factor from the CCG was the level of deprivation and health inequalities for the area. In this group, 79.3% were in the most deprived quintiles (English Index of Multiple Deprivation 2015). Despite the concern that other screening models have a healthy volunteer effect, these individuals are mostly from the lowest socioeconomic status, suggesting this model includes those most at risk from health inequalities.

Although taking individuals with COPD and emphysema may be an appropriate group to target, the sample size is too

Table 1 Descriptive statistics of weight change profile

ID	Age	Sex	PS	Pack years	TNM	Stage	Pathology	MDT	Treatment
1*	68	F	1	15	cT1aN0M0	IA	Lepidic adenocarcinoma	Reduced lung function	SABR
2*					cT2aN0M0	IA	Clinical	Reduced lung function	SABR
3	74	F	1	41	pT1bN0	IA	Adenocarcinoma – acinar		Surgery
4	66	M	1	52	cT1bN0M0	IA	Clinical	ILD	SABR
5*	65	F	1	34	cT1bN0M0	IA	Squamous	Reduced lung function	Radical radiotherapy
6*					cT1aN0M0	IA	Clinical	Reduced lung function	SABR
7	74	M	1	10	cT1bN0M0	IA	Clinical	Site – unable to biopsy. ILD	SABR
8	60	M	3	45	cT1cN0M0	IA	Clinical	Site – unable to biopsy. Multiple comorbidities	SABR
9	70	F	2	43	cT1bN0M0	IA	Clinical	Multiple comorbidities	SABR referral
10	74	M	2	28	cT2aN0M0	IB	Adenocarcinoma	Reduced lung function	SABR
11	67	M	1	45	pT2aNx	IB	Adenocarcinoma – solid		Surgery
12	72	M	1	100	cT2aN0M0	IB	Adenocarcinoma	Multiple comorbidities	SABR
13	71	F	1	55	cT2aN0M0	IB	Adenocarcinoma	Multiple comorbidities. Site – unable to biopsy or give radical radiotherapy or SABR	Palliative radiotherapy
14	74	F	0	22	pT3N0	IIB	Adenocarcinoma – solid		Surgery
15	60	M	1	80	cT4N0M0	IIIA	Squamous		Concurrent chemoradiotherapy
16	67	M	1	75	cT2N2M0	IIIA	Adenocarcinoma		Concurrent chemoradiotherapy
17	68	F	1	10	cT4N1M0	IIIA	Adenocarcinoma		Sequential chemotherapy +CHART
18	65	F	1	63	cT3N2M0	IIIB	Adenocarcinoma		Concurrent chemoradiotherapy
19	66	M	0	50	cT4N2M0	IIIB	Adenocarcinoma		Concurrent chemoradiotherapy
20	62	M	1	51	cT3N3M0	IIIC	Adenocarcinoma		Palliative Immunotherapy
21	64	M	0	52	cT3N2M1c	IVB	Squamous		Palliative chemotherapy

* cancers in the same patient

† cancers in the same patient

ILD, interstitial lung disease; MDT, multidisciplinary team; PS, performance status; SABR, stereotactic ablative radiotherapy; TNM, tumour node and metastasis (8th edition).

small to assert this. Using the annual COPD review appears to be an efficient use of the service, but further work is needed to address missing data regarding uptake of LDCT invitation. Smoking cessation, psychological impact and health economics are other aspects of the ongoing study evaluation.

NHS England has announced plans for targeted LHC in 10 CCGs across the country, which would include LDCT,⁹ and we eagerly await the results. In the meantime, we will continue our current model. We have demonstrated that this can be established within routine NHS clinical practice engaging individuals from deprived areas with a lung cancer prevalence of 2% with improvements in stage of disease.

Acknowledgements S Athey, consultant thoracic radiologist, for all radiology reporting and multidisciplinary team radiology lead. J Hunter, associate clinical lead and GP cancer lead for South Tyneside Clinical Commissioning Group, for service concept and development.

Contributors Service concept and development: EF, JH. Service operation and delivery by South Tyneside Clinical Commissioning Group and South Tyneside and Sunderland NHS Foundation Trust: EF, JH, SA, TR, HG. Radiology reporting by South Tyneside and Sunderland NHS Foundation Trust: SA. Analysis of data: HG, TR. Drafting of manuscript: HG, TR, EF. Guarantors of overall content: HG, TR, EF. Review, revision and agreement of final manuscript: All authors.

Funding Northern Cancer Alliance contributed towards funding for HG and TR respiratory research fellow post. The programme is commissioned by South Tyneside Clinical Commissioning Group.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Helen Grover <http://orcid.org/0000-0002-6010-1933>

REFERENCES

- 1 Public Health England. National cancer registration and analysis service. Available: <https://www.cancerdata.nhs.uk/dashboard/lung.html#?tab=Overview&ccg=00N> [Accessed 25 Oct 2019].
- 2 Public Health England. Health profile for England, 2018. Available: <https://www.gov.uk/government/publications/health-profile-for-england-2018/chapter-5-inequalities-inhealth> [Accessed 2 Oct 2019].
- 3 McDonald FE, Yadeegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res* 2014;7:362–71.
- 4 The NHS Atlas of Variation in Healthcare. Reducing unwarranted variation to increase value and improve quality, 2016. Available: https://fingertips.phe.org.uk/documents/Atlas_2015%20Compendium.pdf [Accessed 25 Oct 2019].
- 5 Maldonado F, Bartholmai BJ, Swensen SJ, et al. Are airflow obstruction and radiographic evidence of emphysema risk factors for lung cancer? A nested case-control study using quantitative emphysema analysis. *Chest* 2010;138:1295–302.
- 6 Sanchez-Salcedo P, Wilson DO, de-Torres JP, et al. Improving selection criteria for lung cancer screening. The potential role of emphysema. *Am J Respir Crit Care Med* 2015;191:924–31.
- 7 Royal College of Physicians. National chronic obstructive pulmonary disease (COPD) audit programme: primary care report for England 2014–15, 2016. Available: <https://www.rcplondon.ac.uk/projects/outputs/primary-care-copd-england-finding-measuresuccess> [Accessed 29 Oct 2019].
- 8 Callister MEJ, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015;70 Suppl 2:i1–54.
- 9 NHS England. NHS to rollout lung cancer scanning trucks across the country, 2019. Available: <https://www.england.nhs.uk/2019/02/lung-trucks/> [Accessed 16 Oct 2019].

Archives of Disease in Childhood

Showcasing the best in paediatric medicine

Official journal of the Royal College of Paediatrics and Child Health, *Archives of Disease in Childhood (ADC)*, brings you the latest advances in childhood disease diagnostics and treatment, inclusive of the perinatal period through to adolescence.

Why read?

- **Get 3 for the price of 1** with one subscription for **ADC**, **ADC Fetal and Neonatal edition**, and **ADC Education and Practice edition**
- **Stay up-to-date with the latest therapies** in our quarterly Paediatric and Perinatal Drug Therapy supplement
- **Read high-quality, original research**, on community child health, public health, epidemiology, acute paediatrics, advocacy, and ethics.
- **Access Archimedes** for evidence-based, clinical problem-solving articles
- **Choose how to access information** with our multimedia content, including podcasts, blogs and social channels



Find out more
adc.bmj.com

RCPCH
Royal College of
Paediatrics and Child Health
Leading the way in Children's Health

BMJ

Join our online communities:

[@qADC_BMJ](https://twitter.com/qADC_BMJ) [/ADC.BMJ](https://www.facebook.com/ADC.BMJ)

Única associação ICS/LABA com 24h de eficácia contínua através de 1 inalação/dia^{1,2}

O perfil de segurança de Revinty foi validado em ensaios clínicos de grande escala, como o SUMMIT (n=4121) e SLS na Asma (n=2114)^{3,4}



ICS | LABA



1 inalação²



1 vez ao dia²



1 dispositivo



Referências: 1. Bernstein DI et al. Fluticasone furoate (FF)/ vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. J Asthma. 2015;52(10):1073-1083. 2. RCM Revinty Ellipta, dezembro 2018. 3. Woodcock A et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open label, parallel group, randomised controlled trial. Lancet 2017; doi.org/10.1016/S0140-6736(17)32397-8. 4. Vestbo J et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet 2016;387:1817-1826.

Legenda: ICS - Corticosteroide inalado; LABA - Agonista β_2 de longa ação; SLS - Salford Lung Study

NOME DO MEDICAMENTO Revinty Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Revinty Ellipta 92/22 μ g: Cada inalação disponibiliza uma dose administrada de 92 μ g de furoato de fluticasona e 22 μ g de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 100 μ g de furoato de fluticasona e 25 μ g de vilanterol (como trifenatato). Revinty Ellipta 184/22 μ g: Cada inalação disponibiliza uma dose administrada de 184 μ g de furoato de fluticasona e 22 μ g de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 200 μ g de furoato de fluticasona e 25 μ g de vilanterol (como trifenatato). FORMA FARMACÊUTICA Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÊUTICAS** Asma: Revinty Ellipta 92/22 μ g e 184/22 μ g está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista beta2 de ação prolongada e corticosteroides para inalação) é adequada: doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas beta2 de curta duração de ação "conforme o necessário"; doentes que estão já adequadamente controlados com corticosteroide para inalação e agonista beta2 de longa duração de ação. **DPOC:** Revinty Ellipta 92/22 μ g está indicado para o tratamento sintomático de adultos com DPOC com um FEV₁ previsível normal <70% (após o broncodilatador) com antecedentes de exacerbação apesar da terapêutica regular com um broncodilatador. **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Asma (92/22 μ g e 184/22 μ g) **Adultos e adolescentes ≥ 12 anos** Deve considerar-se uma dose inicial de uma inalação de 92/22 μ g uma vez por dia para adultos e adolescentes ≥ 12 anos que requeiram uma dose média de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 μ g, a dose pode ser aumentada para 184/22 μ g. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controle efetivo dos sintomas. Revinty Ellipta 184/22 μ g deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controle dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser tomado um agonista beta2 de curta duração, por inalação, para o alívio imediato. A dose máxima recomendada é 184/22 μ g 1x/dia. **Crianças <12 anos** A segurança e a eficácia ainda não foram estabelecidas na indicação para a asma. **DPOC (92/22 μ g) Adultos ≥ 18 anos** Uma inalação 1x/dia. Os doentes normalmente verificam uma melhoria na função pulmonar 16-17 minutos após a inalação. **População pediátrica** Não é relevante na população pediátrica para a indicação de DPOC. **Populações especiais Idosos (> 65 anos)** e **Compromisso renal** Não é necessário ajustar a posologia. **Compromisso hepático** Estudos revelaram um aumento na exposição sistêmica ao FF. Devem tomar-se precauções na definição da posologia em doentes com compromisso hepático que possam estar em risco mais elevado de reações adversas sistêmicas associadas a corticosteroides. Para os doentes com compromisso hepático moderado ou grave a dose máxima é 92/22 μ g. **Modo de administração** Via inalatória. Deve ser administrado à mesma hora do dia, todos os dias. Se uma dose for omitida, deve tomar-se a próxima dose à hora habitual no dia seguinte. Após inalação, os doentes devem enxaguar a boca com água sem a engolir. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO** **Deterioração da doença** Não deve ser utilizado para tratar sintomas de asma aguda ou uma exacerbação aguda na DPOC, para os quais é necessário um broncodilatador de curta duração. O uso aumentado de broncodilatadores de curta duração para aliviar os sintomas indica deterioração do controle. Os doentes não devem interromper a terapêutica na asma ou na DPOC, sem supervisão de um médico, uma vez que os sintomas podem reaparecer após a descontinuação. Os acontecimentos adversos e as exacerbações relacionadas com a asma podem ocorrer durante o tratamento. Deve pedir-se aos doentes que continuem o tratamento mas que procurem aconselhamento médico se os sintomas da asma continuarem incontroláveis ou piorarem após o início do tratamento com Revinty Ellipta. **Broncospasmo paradoxal** Pode ocorrer com um aumento imediato na pieira após a administração. Deve ser tratado imediatamente com um broncodilatador para inalação de curta duração. Revinty Ellipta deve ser suspenso imediatamente, o doente avaliado e uma terapêutica alternativa instituída conforme o necessário. **Efeitos cardiovasculares** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas por ex., taquicardia supraventricular e extra-sístoles. Num estudo controlado com placebo em indivíduos com DPOC moderada e com antecedentes, ou um risco aumentado de doença cardiovascular, não existiu aumento do risco de acontecimentos cardiovasculares. No entanto, deve ser utilizado com precaução em doentes com doença cardiovascular grave ou anomalias do ritmo cardíaco, tireotoxicose, hipocalcemia não corrigida ou em doentes com predisposição para níveis baixos de potássio sérico. **Doentes com compromisso hepático** Para os doentes com compromisso hepático moderado a grave, deve ser utilizada a dose de 92/22 μ g. **Efeitos sistêmicos dos corticosteroides** Podem ocorrer com qualquer corticosteroide para inalação, em especial com doses elevadas recetadas durante longos períodos (ocorrência muito menos provável do que com corticosteroides orais). Incluem síndrome de Cushing, características cushingoides, apoplexia suprarrenal, diminuição na densidade mineral óssea, retardação do crescimento em crianças e adolescentes, cataratas e glaucoma e, mais raramente, uma variedade de efeitos psicológicos e comportamentais incluindo hiperatividade psicomotora, perturbações do sono, ansiedade, depressão ou agressão (em especial em crianças). Administrar com precaução em doentes com tuberculose pulmonar ou em doentes com infecções crônicas ou não tratadas. **Perturbações visuais** Podem ser notificadas perturbações visuais com o uso sistêmico e tóxico de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser considerado para encaminhamento para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, como coriorretinopatia serosa central (CRSC), que foram notificadas após o uso de corticosteroides sistêmicos e tópicos. **Hiperglicemia** Notificados casos de aumentos nos níveis de glicose no sangue em doentes diabéticos e tal deve ser considerado quando se receita a doentes com antecedentes de diabetes mellitus. **Pneumonia em doentes com DPOC** Um aumento da incidência de pneumonia, incluindo pneumonia que requer hospitalização, tem sido observado nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de um risco aumentado de pneumonia com o aumento da dose de esteroide mas isto não foi demonstrado de forma conclusiva entre todos os estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infecções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, índice de massa corporal (IMC) baixo e DPOC grave. Pneumonia em doentes com asma A incidência de pneumonia em doentes com asma foi frequente na dose mais elevada. A incidência de pneumonia em doentes com asma a tomar 184/22 μ g foi numericamente superior quando comparada com aqueles a receber 92/22 μ g ou placebo. Não foram identificados fatores de risco. **Excipientes** Cada dose administrada contém aproximadamente 25 mg de lactose (na forma mono-hidratada). Doentes com problemas hereditários raros de intolerância à lactose, deficiência total de lactase ou malabsorção de glucose-galactose não devem utilizar este medicamento. **EFETOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram cefaleia e nasofaringite. Com a exceção de pneumonia e fraturas, o perfil de segurança foi semelhante em doentes com asma e DPOC. Durante os estudos clínicos, pneumonia e fraturas foram mais frequentemente observadas em doentes com DPOC. **Infeções e infestações** Frequentes - Pneumonia, infecção do trato respiratório superior, bronquite, gripe, candidíase da boca e da garganta. **Doenças do sistema imunitário** Raras - Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária. **Perturbações do foro psiquiátrico** Raras - Ansiedade. **Doenças do sistema nervoso** Muito frequentes - Cefaleia. Raras - Tremor. **Afeções oculares** Pouco frequentes - Visão turva. **Doenças cardíacas** Pouco frequentes - Extra-sístoles. Raras - Palpitações, taquicardia. **Doenças respiratórias, torácicas e do mediastino** Muito frequentes - Nasofaringite. Frequentes - Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia. Raras - Broncospasmo paradoxal. **Doenças gastrointestinais** Frequentes - Dor abdominal. **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes - Artralgia, dorsalgia, fraturas, espasmos musculares. **Perturbações gerais e alterações no local de administração** Frequentes - Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **DATA DA REVISÃO DO TEXTO** dezembro 2018. **APRESENTAÇÃO:** Revinty Ellipta 92 μ g+22 μ g, 30 doses; Revinty Ellipta 184 μ g+22 μ g, 30 doses. Regime de comparticipação: Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial-Portela & C^o, S.A., -À Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. DDVSAM190129 RV/SET19/010 PM-PT-FFV-JRNA-190001, setembro 2019