Emergency management of immune-related toxicities

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@acutemed2

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Overview

- Models of emergency care for immune-related toxicities
- Case studies immune-related toxicities
- Current guidelines
- Approach to an emergency patient being treated with ICIs

Emergency Oncology Models

Support Care Cancer
DOI 10.1007/s00520-016-3470-1

COMMENTARY

Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley[1] · Terry Rice[2]

Cooksley T, Rice T. *Supportive Care in Cancer* 2017

Emergency Oncology Models

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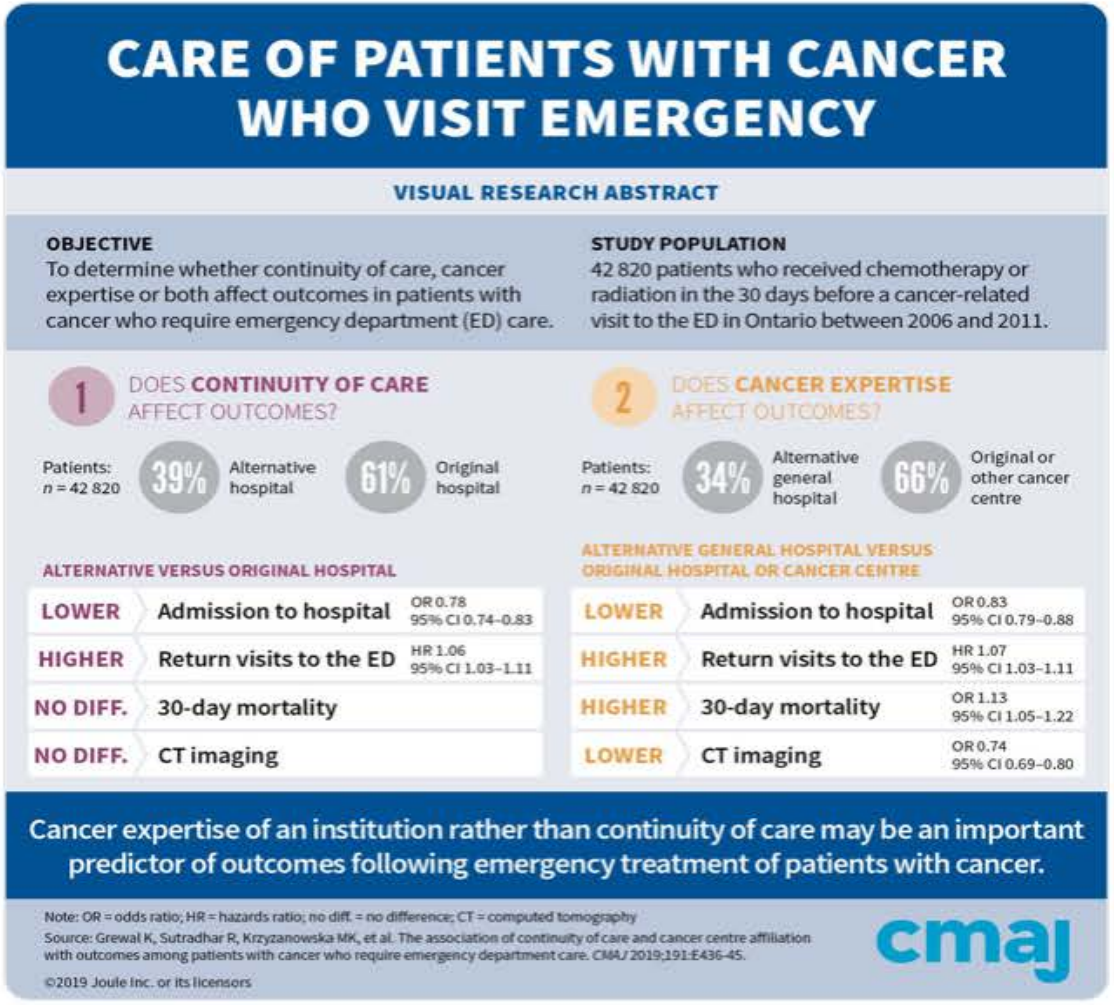
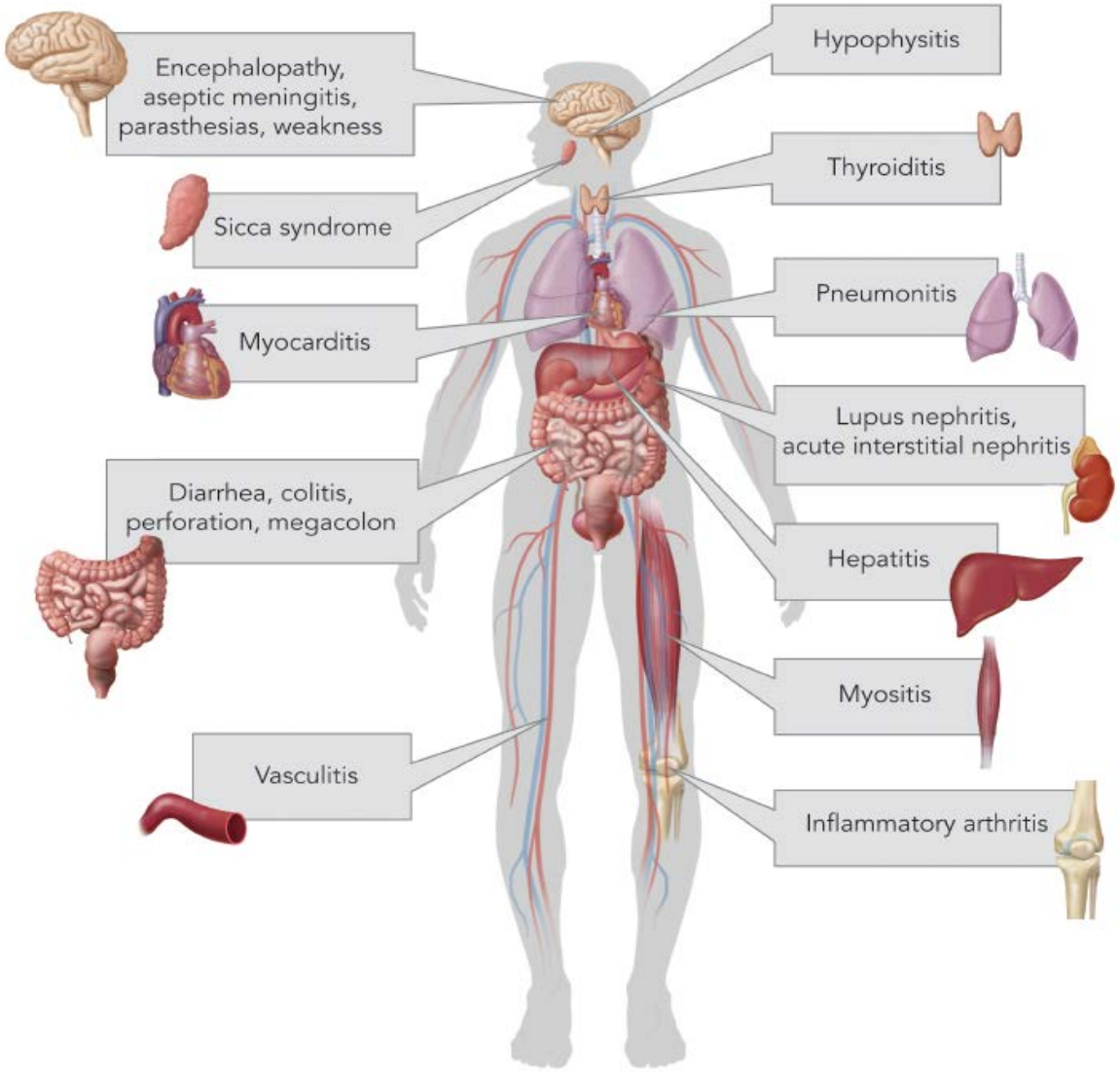
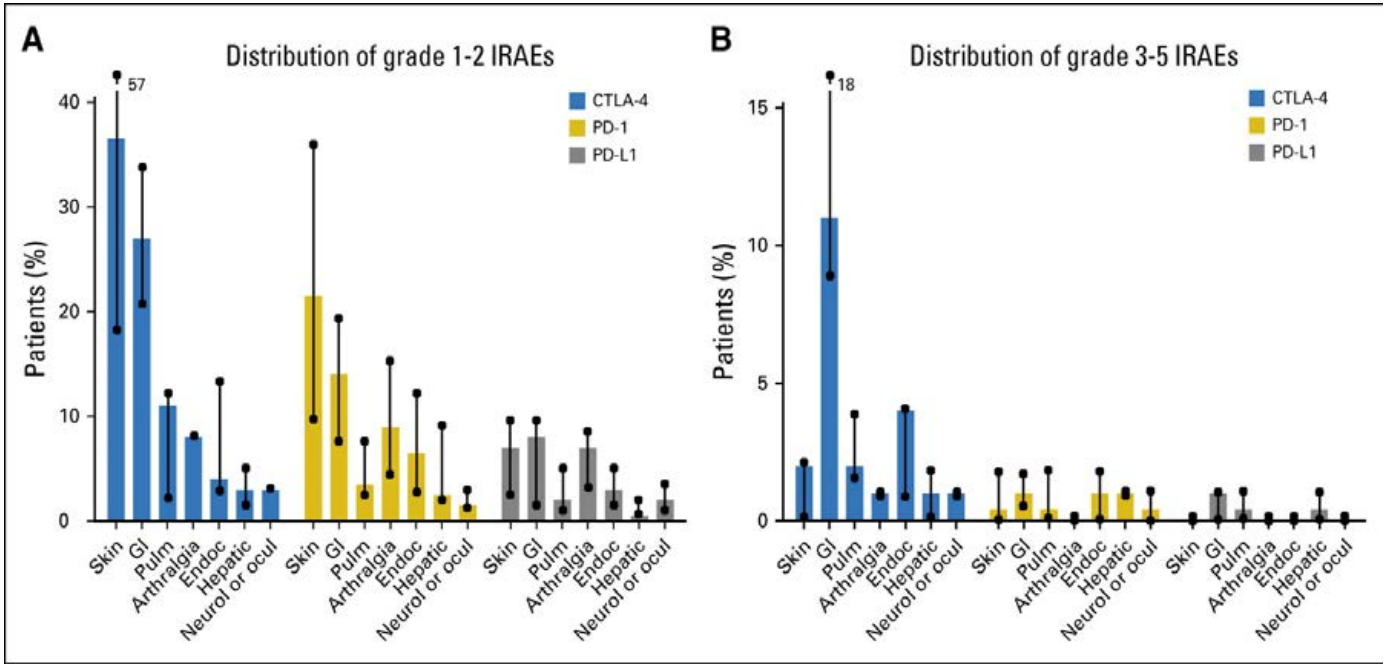


Immune-related toxicities



Dirzeno et al. The Rheumatologist

Frequency of IR Toxicities



Brahmer et al 2018. ASCO

Emergency presentation data

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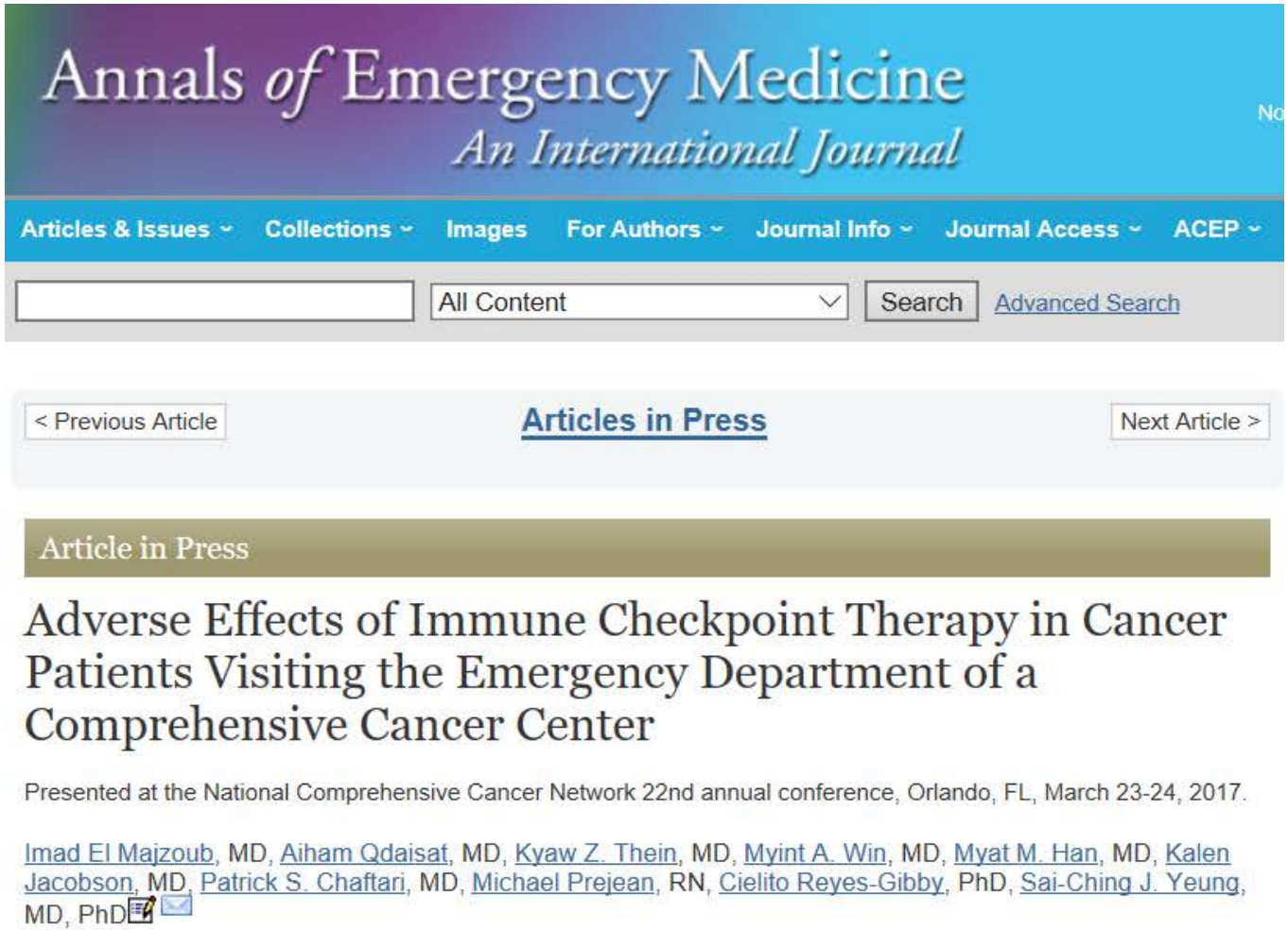

Annals of Emergency Medicine
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Article in Press

Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center

Presented at the National Comprehensive Cancer Network 22nd annual conference, Orlando, FL, March 23-24, 2017.

Imad El Majzoub, MD, Aiham Qdaisat, MD, Kyaw Z. Thein, MD, Myint A. Win, MD, Myat M. Han, MD, Kalen Jacobson, MD, Patrick S. Chaftari, MD, Michael Prejean, RN, Cielito Reyes-Gibby, PhD, Sai-Ching J. Yeung, MD, PhD

Guidelines

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: May 2017.

General approach to IR toxicities

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CTCAE Grade	Management
1	Supportive treatment Close monitoring Investigations to exclude other cause of symptoms Patient advice and education
2	As per grade with the addition of:- Withhold checkpoint inhibitor until symptoms settle/resolve If symptoms persist for >5 days consider oral prednisolone Liaison with Oncology and Organ-related specialist
3/4	Supportive treatment Commence high dose steroids (1-2mg/kg OD IV Methylprednisolone) Withhold checkpoint inhibitor Investigations to exclude other cause of symptoms and assess severity Liaison with Oncology and Organ-related specialist If symptoms persist despite steroids consider additional immunosuppressive agent

Case Study

- 54 year old male
- Metastatic melanoma
- Completed 3 cycles of Ipilimumab
- 4 day history of generalized headache, extreme fatigue and nausea
- Seen 2 days earlier at local Uni hospital
    - CT brain – NAD
    - Diagnosed migraine and discharged

Case Study (Examination)

- Alert
- BP = 100/60mmHg. Pulse = 90bpm
- Chest clear
- No focal neurology
- BM = 2.1mmols

Case Study (Pituitary Profile)

- Cortisol < 50
- TSH = 0.03
- LH < 1
- FSH < 2
- ACTH = 10
- Prolactin = 150

Guidelines

Endocrine CONNECTIONS | C E Higham *et al.* | Acute management of CKI endocrinopathies | 7:5 | G1–G7

EMERGENCY GUIDANCE

SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE

Acute management of the endocrine complications of checkpoint inhibitor therapy

C E Higham[1], A Olsson-Brown[2,3], P Carroll[4], T Cooksley[5], J Larkin[6], P Lorigan[7], D Morganstein[8] and P J Trainer[1] the Society for Endocrinology (SfE) Clinical Committee[9]

[1]Department of Endocrinology, Christie Hospital NHS Foundation Trust, Manchester, Centre for Endocrinology and Diabetes, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[2]The Clatterbridge Cancer Centre, Bebbington, Wirral, UK
[3]The University of Liverpool, Brownlow Hill, Liverpool, UK
[4]Department of Endocrinology, Guy's & St. Thomas' NHS Foundation Trust, London, UK
[5]Department of Acute Medicine, UHSM and Christie Hospital NHS Foundation Trust, Manchester, UK
[6]Skin Unit, Royal Marsden Hospital, London, UK
[7]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK
[8]Department of Endocrinology, Chelsea and Westminster Hospital, London, UK
[9]The Society for Endocrinology, Woodlands, Bradley Stoke, Bristol, UK

Guidance for life-threatening immune-related HPA toxicity

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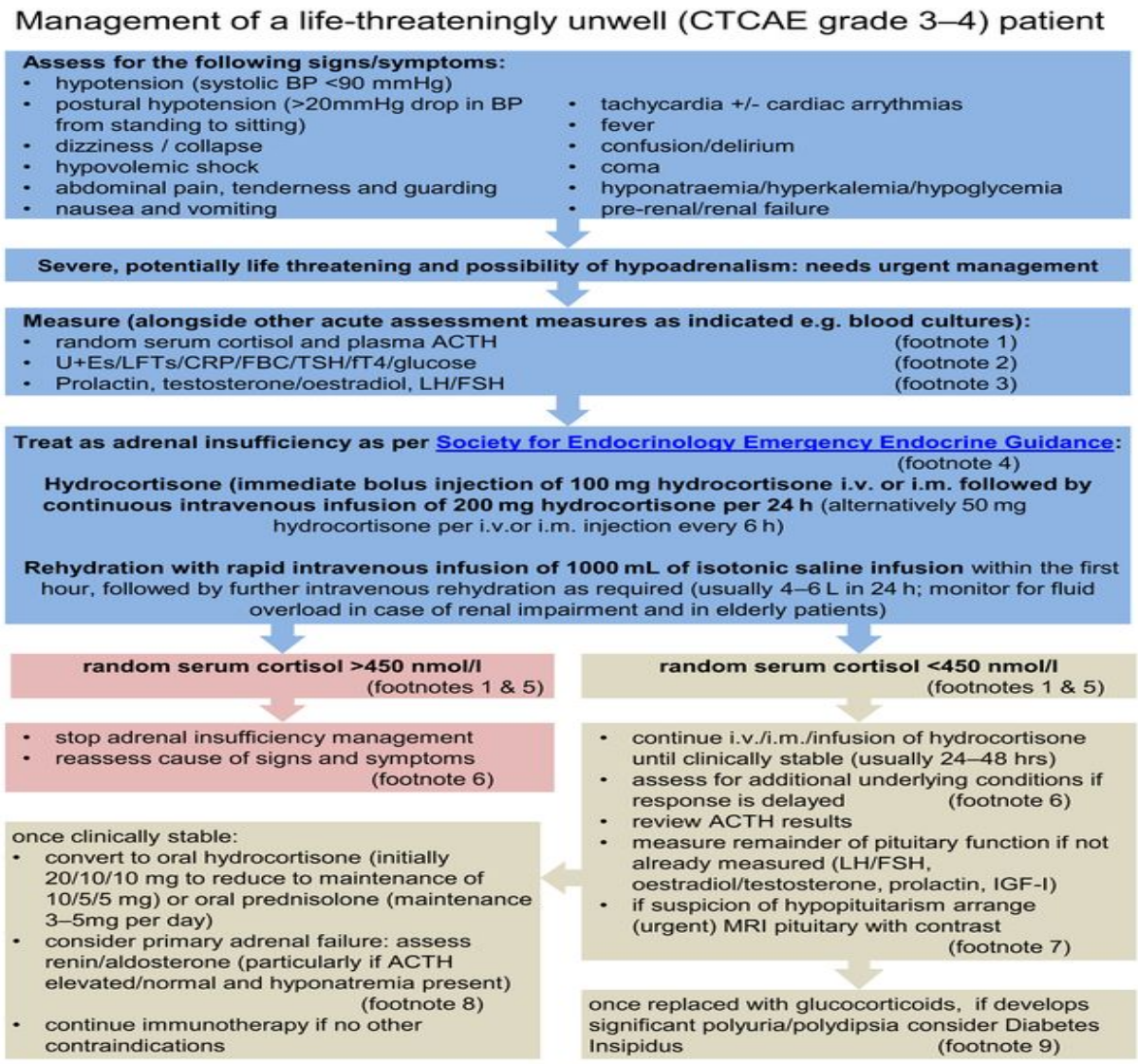

Steroid management of IR HPA toxicity

Cancer

Original Article

High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma

Alexander T. Faje MD ✉, Donald Lawrence MD, Keith Flaherty MD, Christine Freedman RN, Riley Fadden NP, Krista Rubin NP, Justine Cohen MD, Ryan J. Sullivan MD

First published: 05 July 2018 | https://doi.org/10.1002/cncr.31629 | Cited by: 4

Collaboration is key

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Cancer

Correspondence

Emergency management of immune-related hypophysitis: Collaboration between specialists is essential to achieve optimal outcomes

Tim Cooksley MBChB (Hons), MRCP (Acute), Claire Higham MBBS, DPhil, Paul Lorigan MBBCH, FRCP, Peter Trainer MBChB, MD

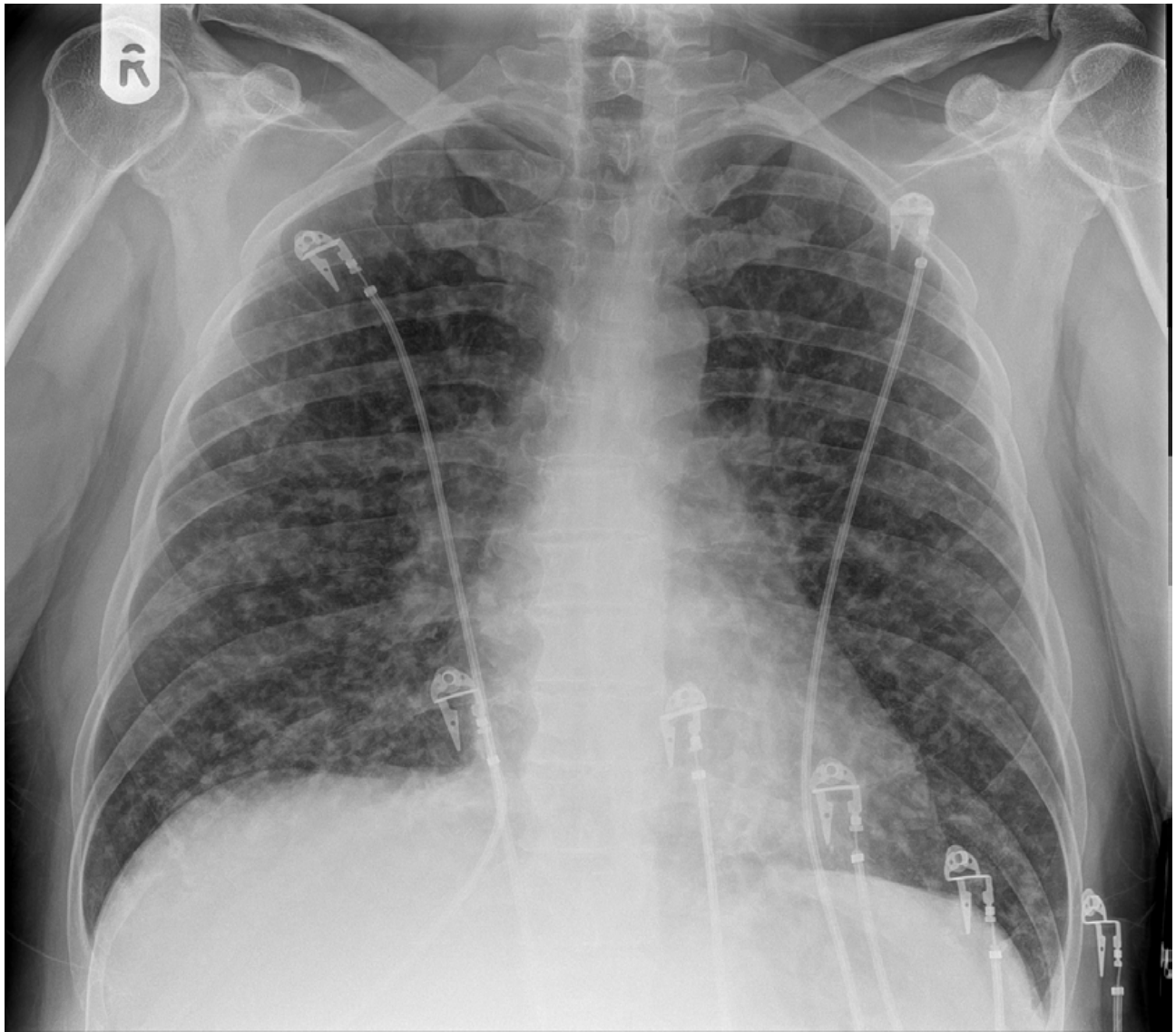
First published: 23 October 2018 | https://doi.org/10.1002/cncr.31789

Case Study

- 47 year old male
- Metastatic melanoma
- Completed 2 cycles of Ipi/Nivo
- Presents with:
  - Severe and rapidly progressively dyspnoea
  - Dry cough
  - Myalgia/fatigue

Clinical examination

- Unwell. Extremely dyspnoeic
- Apyrexial
- BP = 140/70mmHg Pulse =130bpm
- RR = 40 O_2 SATS = 82% (AIR)
- Chest clinically clear
- Abdo and neuro examination unremarkable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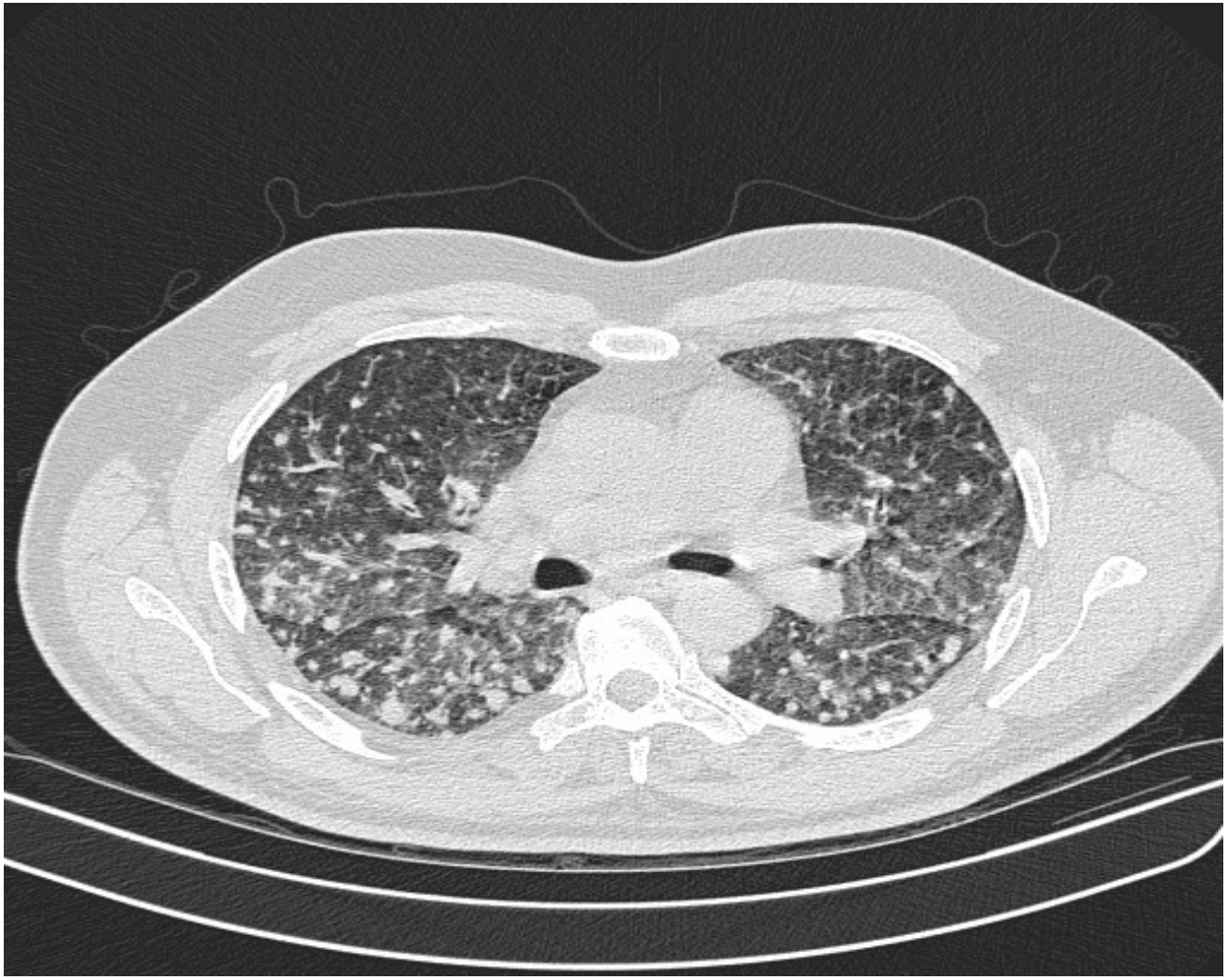
Emergency management

- Cultures – including Viral N+T swabs, PCP screen and β-Glucan
- Urgent HRCT
- Too unwell for bronchoscopy

- High flow Oxygen
- IV Methylprednisolone 2mg/kg - PPI and antimicrobial prophylaxis
- IV Co-Amoxiclav
- Chest physio
- Agreement with ICU colleagues for IPPV if required
- Given IV infliximab (5mg/kg) at 24 hours given severity of illness

Immune-mediated granulomatous pneumonitis



Clinical progress

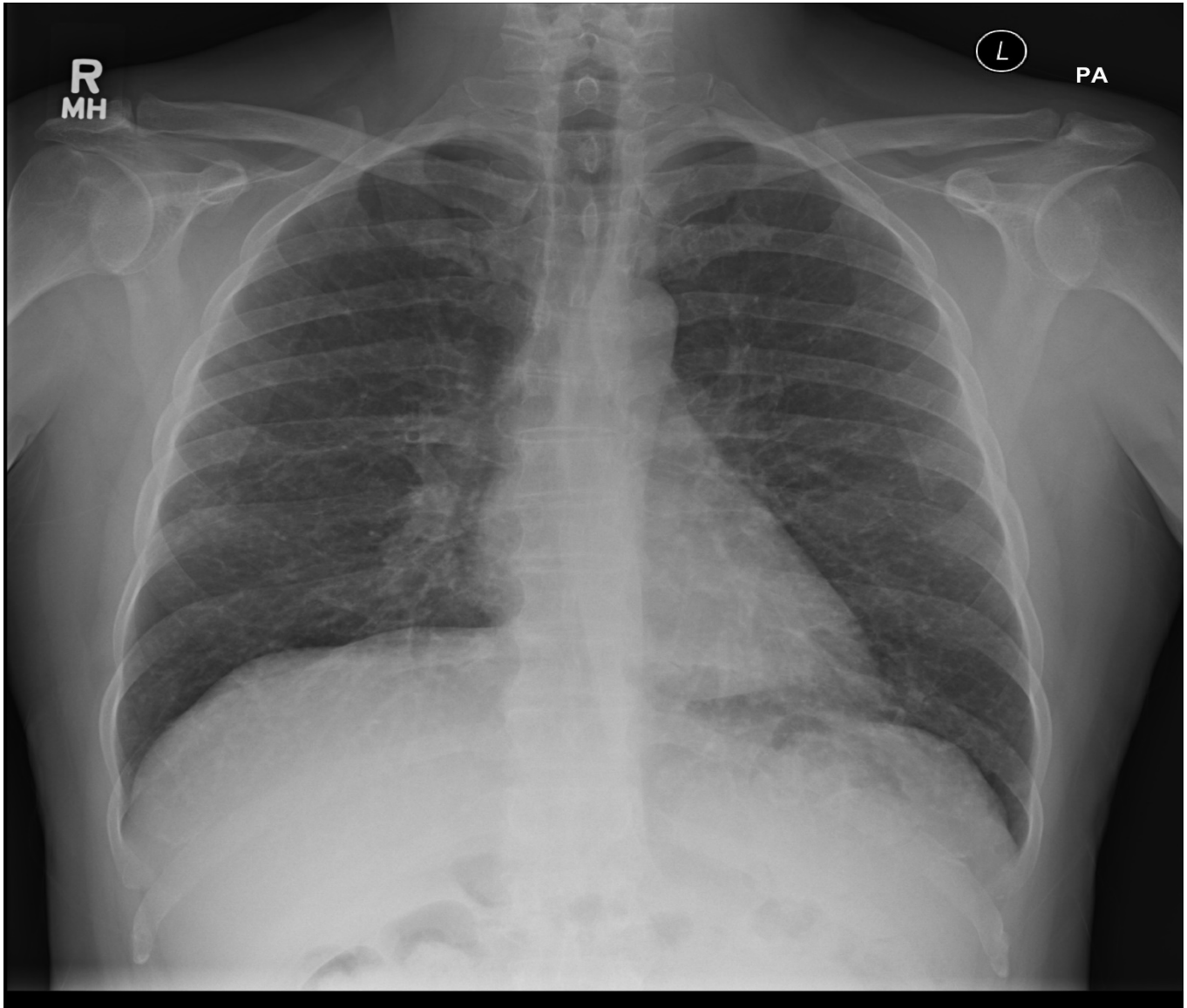
- Excellent clinical progress over 72 hours
- High flow oxygen weaned
- 3 days of IV methylprednisolone (2mg/kg)

- Cultures and β – Glucan negative

- Weaned to oral prednisolone
- Commenced on Mycophenolate Mofetil 500mg BD

- Discharged at 5 days with early clinic follow up

1 week later



Case presentation

- 57 year old male with metastatic papillary renal cell carcinoma
- C1 Ipi/Nivo
- Presents with rapid onset of diplopia

Case presentation

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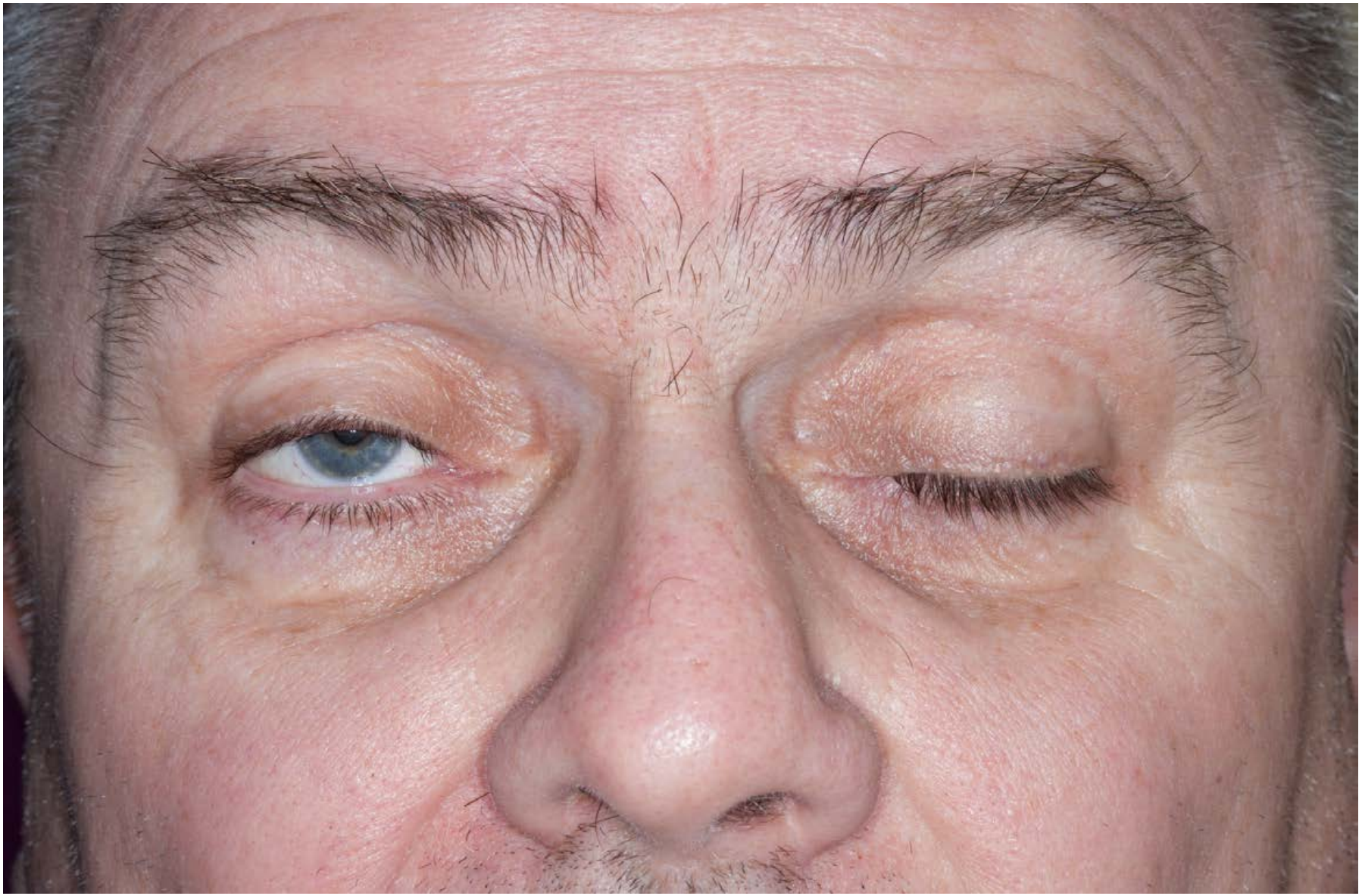

Emergency management

- Commenced on IV methylprednisolone (1mg/kg)
- Pyridostigmine 60mg TDS
- Monitoring FEV1

- EMG – Abnormal jitter analysis in facial muscles

- IV Immunoglobulins (1g/kg)

- Excellent clinical progress
- Converted to weaning oral prednisolone and MMF 500mg BD

JAMA Internal Medicine

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Alternative Strategies to Inpatient Hospitalization for Acute Medical Conditions
A Systematic Review

Jared Conley, MD, PhD, MPH; Colin W. O'Brien, BS; Bruce A. Leff, MD; Shari Bolen, MD, MPH; Donna Zulman, MD, MS

IMPORTANCE Determining innovative approaches that better align health needs to the appropriate setting of care remains a key priority for the transformation of US health care; however, to our knowledge, no comprehensive assessment exists of alternative management strategies to hospital admission for acute medical conditions.

OBJECTIVE To examine the effectiveness, safety, and cost of managing acute medical conditions in settings outside of a hospital inpatient unit.

Conley *et al* 2016, JAMA Intern Med 176(11):1693

Antibiotics and ICIs

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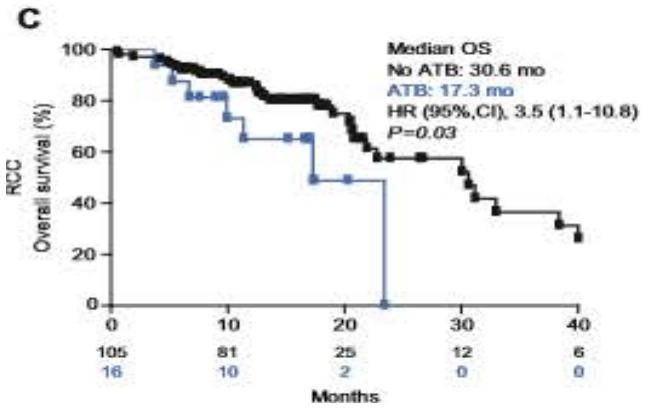
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

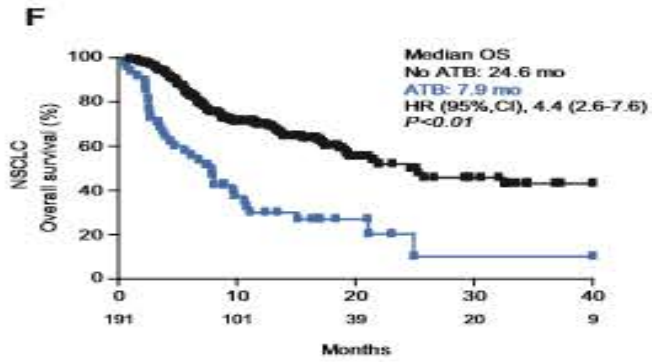
Annals of Oncology 29: 1437–1444, 2018
doi:10.1093/annonc/mdy103
Published online 30 March 2018

ORIGINAL ARTICLE

Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer

L. Derosa[1,2,3†], M. D. Hellmann[4,5,6†], M. Spaziano[7], D. Halpenny[8], M. Fidelle[1,2,3], H. Rizvi[9], N. Long[8], A. J. Plodkowski[8], K. C. Arbour[4], J. E. Chaft[4,5], J. A. Rouche[10], L. Zitvogel[1,2,3,11], G. Zalcman[12], L. Albiges[1,3,13,14], B. Escudier[1,13,14] & B. Routy[1,2,3,15,16*]





Emergency Workup

- Low threshold for considering IR toxicities
- Need thorough clinical work up
- Need to exclude important non-IR related diagnoses

- Early initiation of high dose steroids in those with high clinical suspicion
- Role for early infliximab (anti-TNF) to minimize long-term steroid exposure and reduce morbidity/mortality in life-threatening IR toxicity?

Future research

- Biomarkers for prediction of those at risk
- Biomarkers for detection
- Antibiotic therapy and risk of infection
- RCTs into the optimal management
    - Timing of infliximab/immunosuppression
- Ambulatory management?
    - Is it possible to identify cohort at low risk of complications with Grade 3 toxicity?

Conclusions

- Emergency presentations in patients on checkpoint inhibition are a challenge
- Need to distinguish IR and non-IR presentations
- Research needed into management and pathways of IR toxicities
- Education of patients and health care professionals