Evaluation of immune-related toxicities from an emergency standpoint

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MASCC Conference, Vienna, 28th June 2018

@acutemed2

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Faculty Disclosure

x	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

Overview

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- Models of delivering care for immune-related toxicities
- Description of immune-related toxicities
- Current guidelines
- Approach to an unwell patient on checkpoint inhibition

‘Every system is perfectly designed to achieve the results it obtains’

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- Medicine has 3 key tenets:-
  - Understanding disease biology
  - Discovering effective therapies
  - Ensuring those therapies delivered effectively
- Many factors; system determines performance and need to change its pieces

Supportive Care in Cancer

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

"In what has become a near-weekly ritual, one of us receives an emotionally laden call about the plight of a loved one, colleague or acquaintance with cancer who needs our help to navigate the labyrinth of emergency care. The patient may receive care at our comprehensive cancer center but become "stranded" in an ED outside the often rigid borders between our center and other healthcare systems….

These exercises often end with the caller's tremendous expression of gratitude, thanking us for being "miracle workers". However, it shouldn't take a miracle to communicate and deliver high quality patient-centered care in the ED."

Todd K, Thomas C. *Annals of Emergency Medicine* 2016

Learning from neutropenic sepsis

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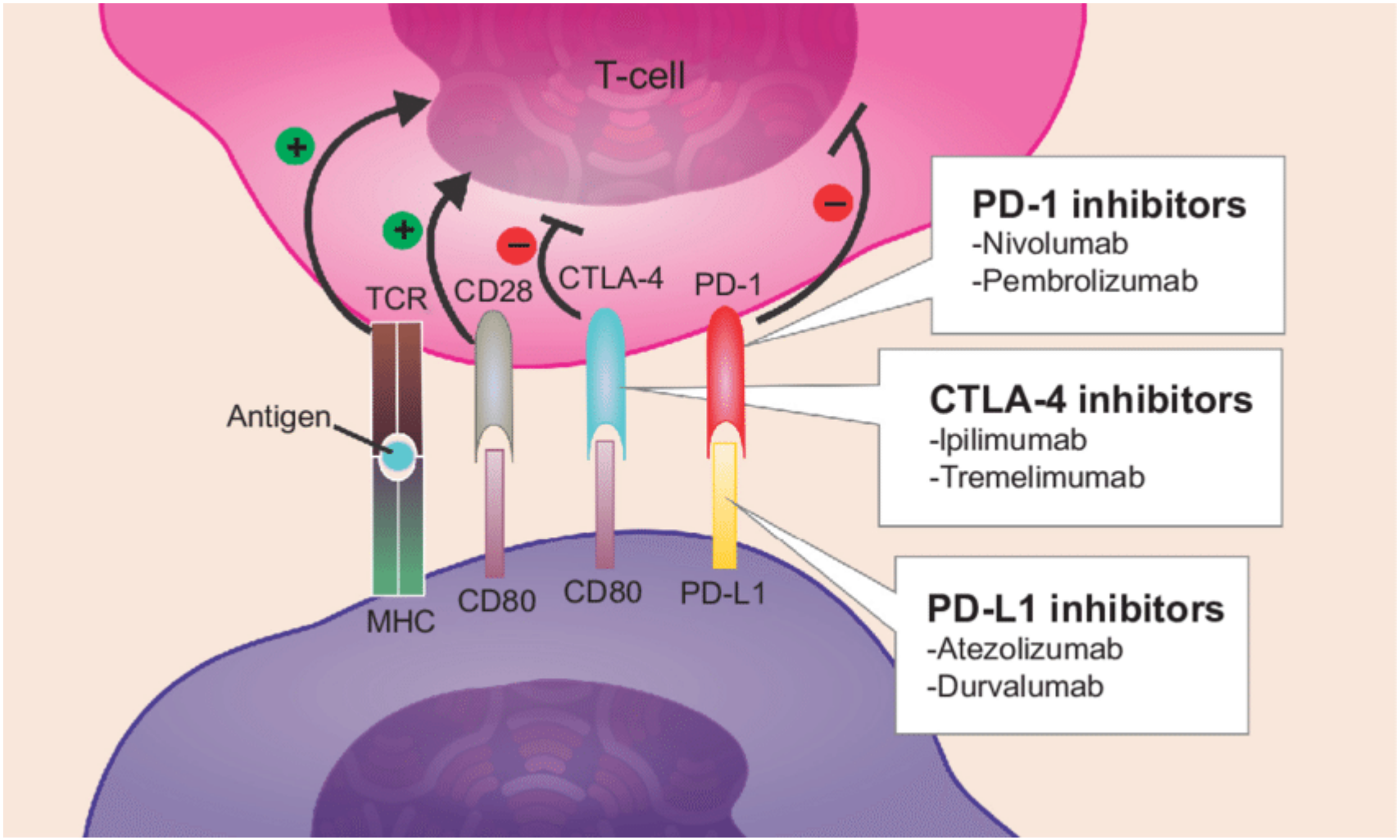
For better, for worse?

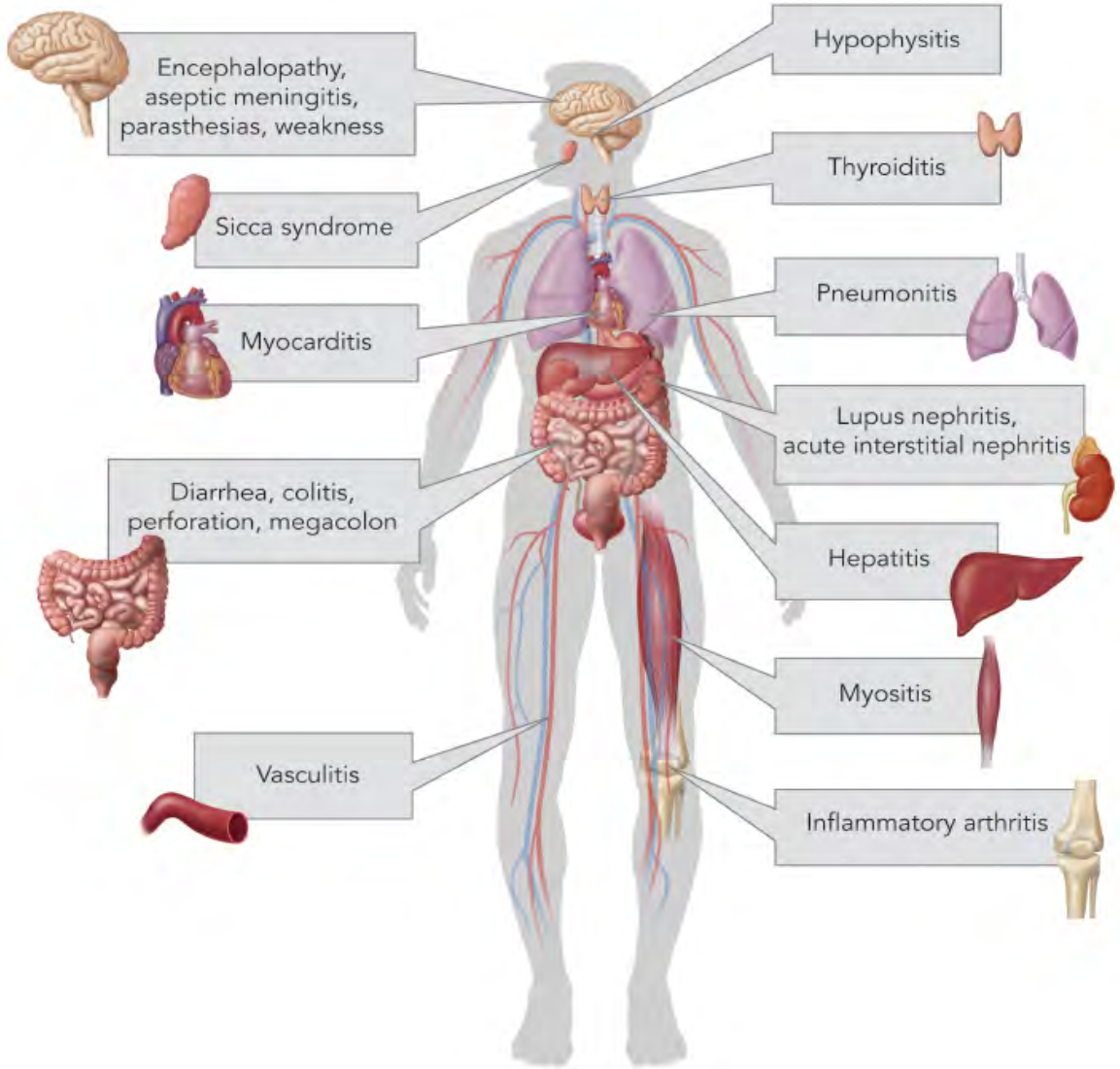
A review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy

Mechanism of checkpoint inhibitors



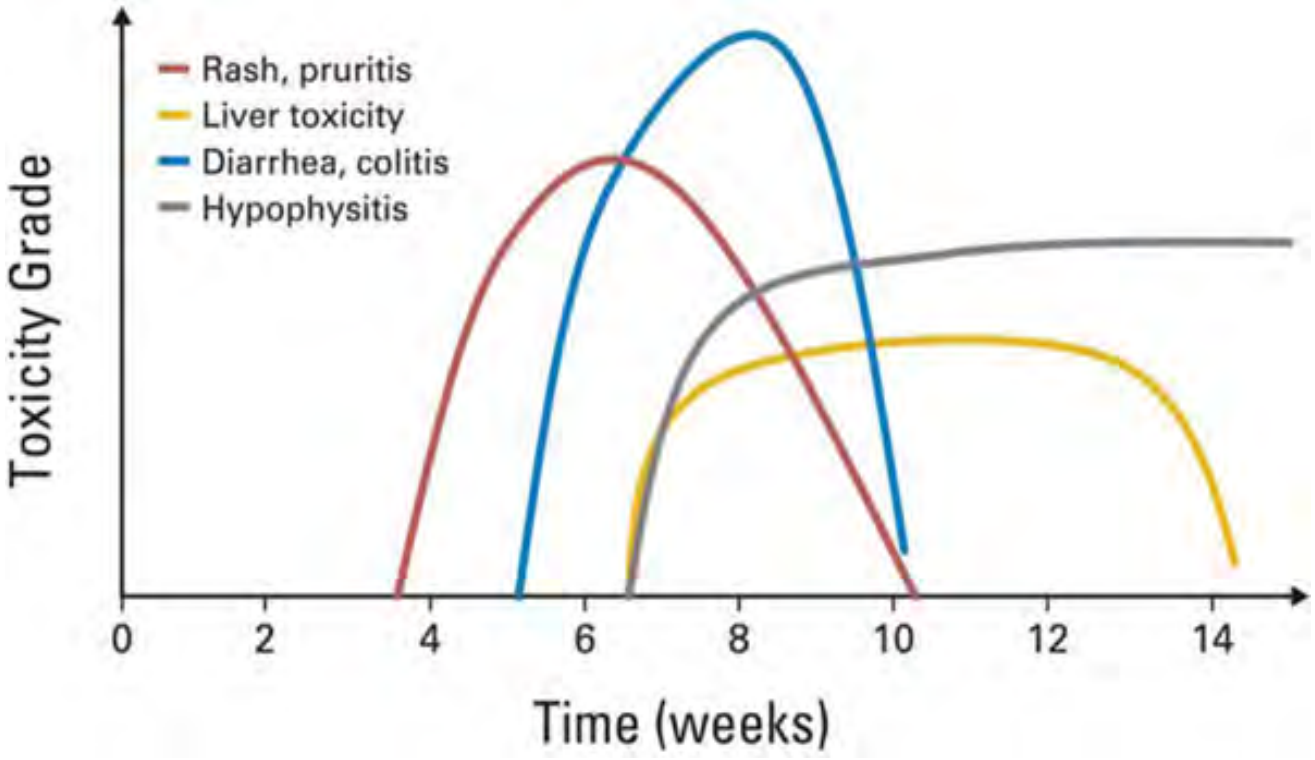
Postow et al 2018 Uptodate

Immune-related toxicities

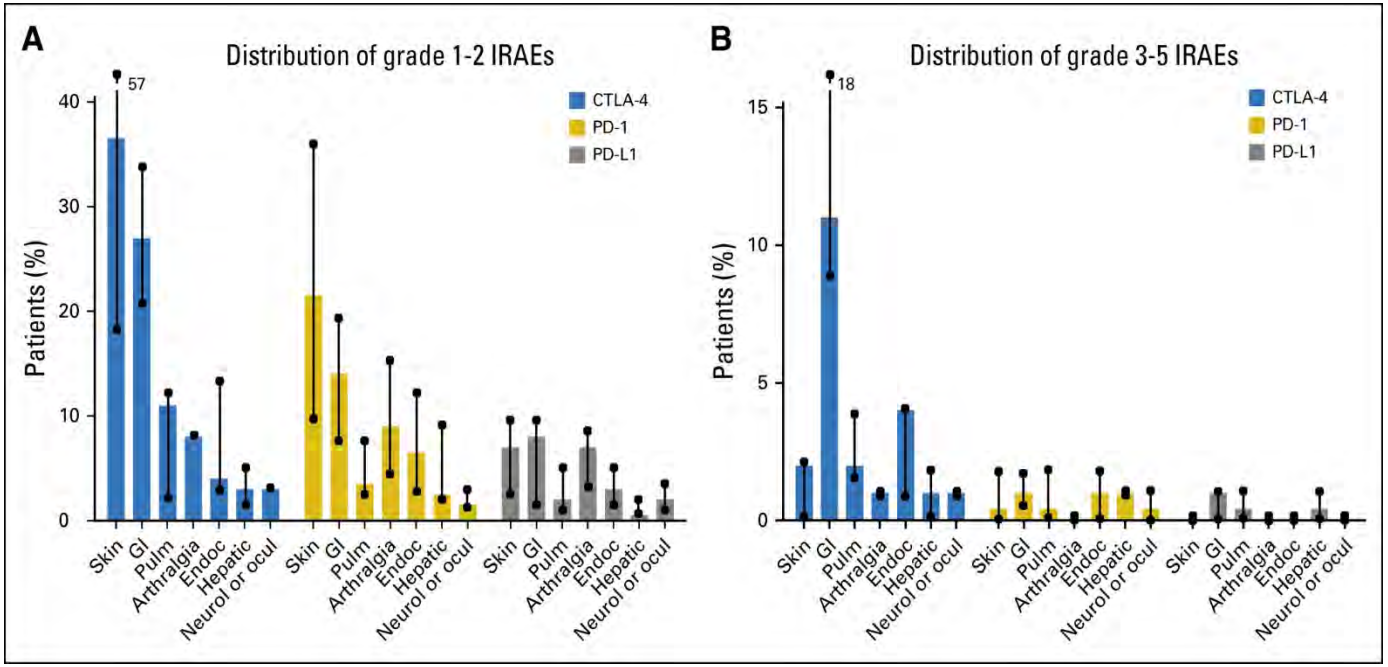


Dirzeno et al. The Rheumatologist

Timing of IR toxicities



Frequency of IR Toxicities



Brahmer et al 2018. ASCO

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

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on February 14, 2018.

Clinical Practice Guideline Committee

A B S T R A C T

Purpose

To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events in patients treated with immune checkpoint inhibitor (ICPi) therapy.

Guidelines

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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.

UKONS Guidelines

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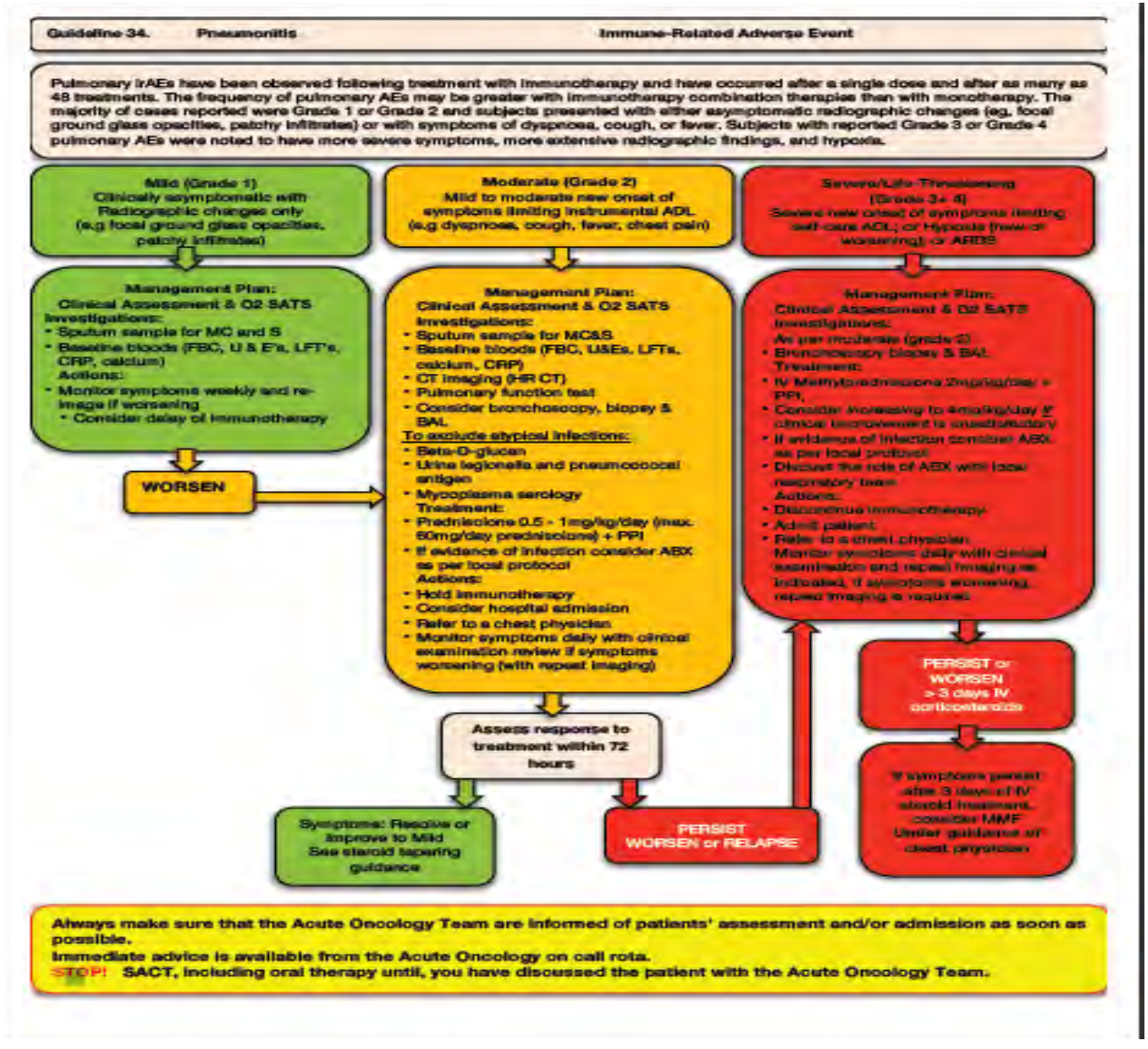

General approach to IR toxicities

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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

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]

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Guidance for life-threatening immune-related endocrinopathy

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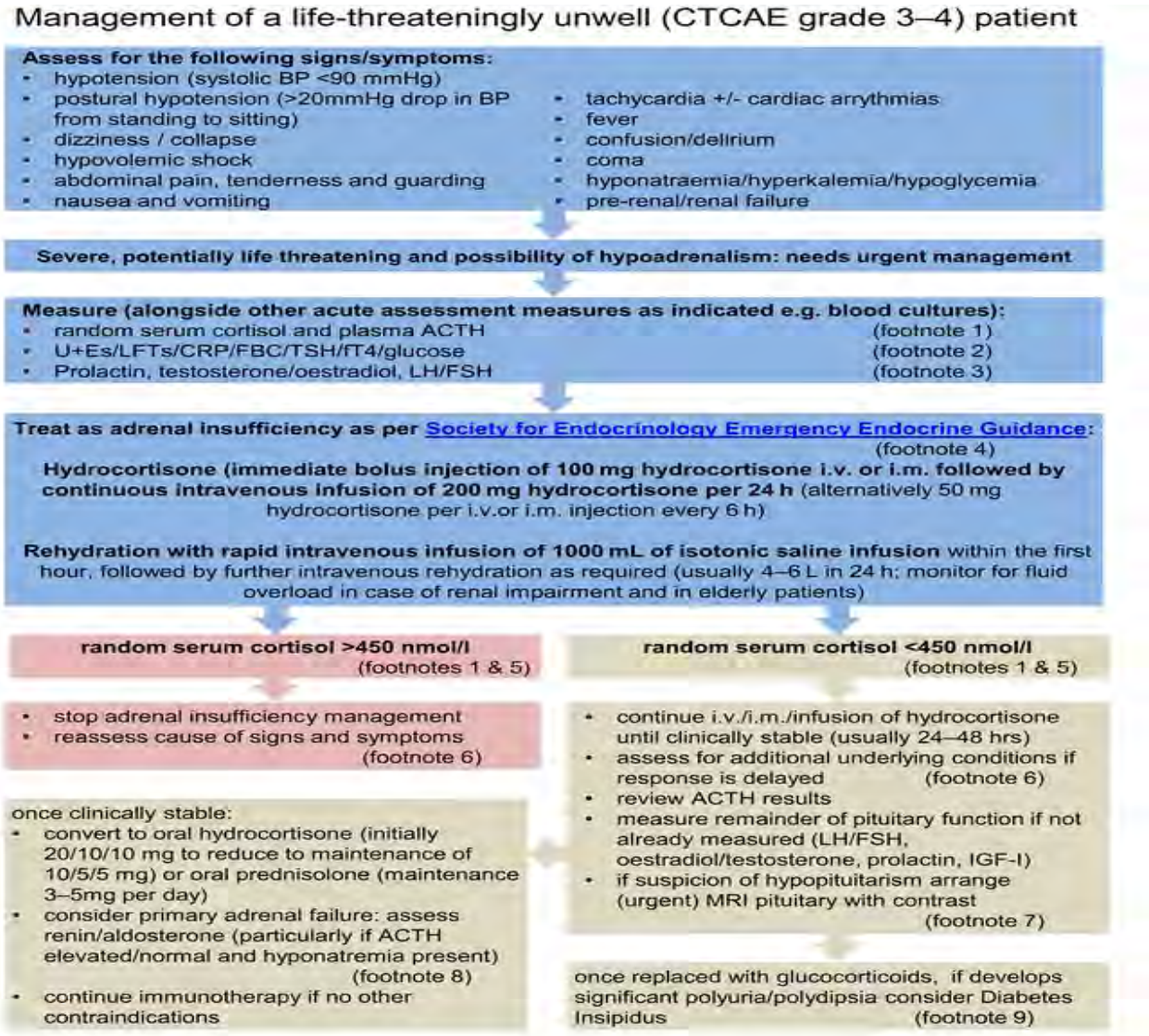

Guidance for possible mild/moderate immune-related endocrinopathy

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Management of patient with mild/moderate symptoms (CTCAE grade 1–2) compatible with cortisol deficiency

- tiredness/fatigue
- weight loss
- susceptibility to infection
- normal BP with no postural drop

mild/moderate: non life-threatening
(may become life-threatening if intermittent illness/physical stress occurs)

measure serum cortisol (ideally at 9 am), and ACTH (footnote 1)

9 am cortisol <200 nmol/l or random cortisol <100 nmol/l **adrenal insufficiency likely**	9 am cortisol 200–450 nmol/l or random cortisol 100–450 nmol/l **adrenal insufficiency possible**	9 am or random cortisol >450 nmol/l **adrenal insufficiency unlikely**
• start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg) • refer to specialist services (Endocrinology) • measure remainder of pituitary profile IGF-1/TSH/fT4/LH+FSH/T2orE2/prolactin For TFT abnormalities see Algorithm 3 • if suspicion of primary adrenal failure or ACTH elevated measure plasma renin and aldosterone • give emergency advice about H/C: https://www.endocrinology.org/adrenal-crisis/ https://doi.org/10.1530/EC-16-0054 • continue immunotherapy if no other contraindications	• refer to Endocrinology • measure remainder of pituitary profile IGF-1/TSH/fT4/LH+FSH/TorE2/prolactin For TFT abnormalities see Algorithm 3 • consider SST (but interpret with caution if ACTH low as may be falsely reassuring in recent onset pituitary disease – discuss with Endocrinology) • continue immunotherapy if no other contraindications • if delay in Endocrine referral anticipated start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg)	• consider other causes of symptoms • continue immunotherapy if no other contraindications

Footnotes:

Footnote 1 Review patient information for evidence of recent steroid use:

- any supraphysiological dose of glucocorticoid can suppress the adrenal axis.
- patients receiving doses of dexamethasone >0.75 mg or prednisolone >3mg daily will likely have a supressed endogenous HPA axis and may have a serum cortisol measurement of <50 nmol/l. If the glucocorticoid treatment is ongoing they are not adrenally insufficient but may need higher doses of glucocorticoids when clinically unwell. Seek specialist advice from endocrinology.

Immune-mediated myocarditis

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

SUMMARY

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt–Ingram Cancer Center Ambassadors and others.)

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

ELSEVIER

Journal of the American College of Cardiology

Volume 71, Issue 16, 24 April 2018, Pages 1755-1764

Original Investigation

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

Syed S. Mahmood MD, MPH [a, b], Michael G. Fradley MD [c], Justine V. Cohen DO [d], Anju Nohria MD [e], Kerry L. Reynolds MD [d], Lucie M. Heinzerling MD, MPH [f], Ryan J. Sullivan MD [d], Rongras Damrongwatanasuk MD [c], Carol L. Chen MD [g], Dipti Gupta MD, MPH [g], Michael C. Kirchberger MD [f], Magid Awadalla MD [b], Malek Z.O. Hassan MD [b], Javid J. Moslehi MD [h], Sachin P. Shah MD [i], Sarju Ganatra MD [i], Paaladinesh Thavendiranathan MD [j], Donald P. Lawrence MD [d] ... Tomas G. Neilan MD, MPH [b, k]

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- 1.14% prevalence of myocarditis
- Median onset of 34 days
- More common in patients on combination checkpoint inhibition
- More common in diabetic patients
- 54% had no other IR toxicities
- 38% of major adverse cardiac events had normal LV
- Lower steroid doses were associated with
  - Higher residual troponin rates
  - Higher major adverse cardiac events

Mahmood S et al . J Am Coll Cardiol 2018

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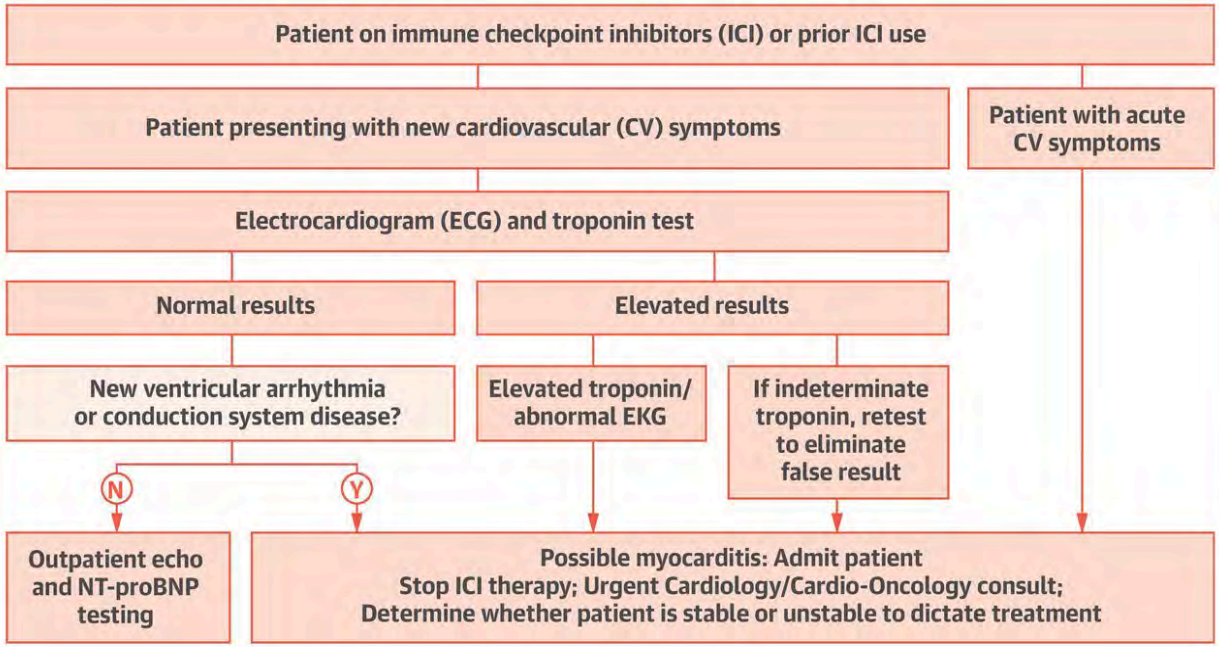
CENTRAL ILLUSTRATION: Algorithm for Work-Up and Management of Immune-Mediated Myocarditis



Mahmood, S.S. et al. J Am Coll Cardiol. 2018;71(16):1755-64.

Case Study

- 62 year old male
- Melanoma
- Completed 3 cycles of adjuvant combination checkpoint inhibition
- History of Type 2 Diabetes and Hypertension
- Presents with dyspnoea
- ECG – Atrial flutter with 2:1 block
- High-Sensitive Troponin – 3,549 ng/L

Case Study

- Urgent Cardiac MRI
- Demonstrates reversible ischaemia in LAD
- No features of IR myocarditis
- Treated for NSTEMI

- Not an immune-related presentation

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?

- Urgently need “real world” data regarding IR and non-IR events presenting as emergencies

Future research

- Biomarkers for prediction of those at risk
- Biomarkers for detection
- Antibiotic therapy and risk of infection
    - GI microbiome may affect risk of IR colitis
    - May affect effectiveness of treatment
- RCTs into the optimal management
    - Timing of infliximab
- Ambulatory management?
    - Is it possible to identify cohort at low risk of complications with Grade 3 toxicity?

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

Disseminating knowledge

- IR toxicities will become more prevalent in non-Oncology hospitals
- Recognition of these complications and knowledge of their management will be increasingly important for non-Oncologists
- Research is needed into the optimal strategies and pathways for their management
- Education of patient and physicians

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
- Real world data required
- Education of patients and health care professionals