Immune-related adverse events in patients treated with immune checkpointsinhibitors: Management in the emergency room

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Immune checkpoints inhibitors (ICIs) are a novel class of drugs used in cancer immunotherapy that are becoming more commonly used among advanced-stage cancers. These ICIs, targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its ligand (PD-L1), have revolutionized the treatment of many different types of cancers and have increased the life expectancy of many patients. However, the inhibition of immune checkpoints may lead to unintended tissue damage which manifests into immune-related adverse effects (irAEs) that seem to arise from increase activity in the immune system.

Emergency physicians are encountering increasing number of patients on these medications as well as the associated side effects and it is important that they have the knowledge to recognize these new averages of complications and how to treat them. Early recognition and treatment of these irAEs may prevent severe complications, inappropriate discharges from emergency room and ICIs discontinuation.

The irAEs can affect nearly every organ system, normally only one but in some special cases the toxicity may present affecting more than one system. The most common irAEs are dermatological, gastrointestinal, endocrine, hepatical and pulmonary; being the cardiological, neurological, ophthalmologic, renal and haematological infrequently reported. Emergency physicians face the challenge of differentiating these irAEs from any other pathology related or not with the underlying cancer. Differential diagnosis in the emergency room may embrace from pathology not related with the underlying cancer, complications of the underlying cancer, cancer progression, opportunistic infections (as long term -> 6 weeks- treatment with immunosupressive drugs increases the chance of opportunistic infections), irAEs affecting one system to irAEs multisystem. The incidence of the irAEs will depend on the ICIs administered and the basal substrate of the patient. In general, irAEs occurs quite early, mostly within weeks to 3 months being

dermatological and gastrointestinal the earliest to manifest. However, physicians must be aware that risk is still present for weeks to months after termination of treatment and that recent history of ICI administration should keep irAE on differential diagnosis. The principle of clinical management of irAEs includes a proacting monitoring, the differential diagnosis, the determination of severity, the management and the follow-up. Both proacting monitoring and follow-up are normally exclusively carried out by oncologist in their specific consultation while the differential diagnosis, determination of severity and acute management may be carried out in the emergency room by more than one specialist. It is important to distinguish the severity of each irAE and quantify by using the Common Terminology Criteria for Adverse Events v4.03 in order to standardize treatment and follow-up of these patients. In general, low-grade irAEs (grade 1-2) are mild to moderate while grades 3-4 are severe or even life-threatening. Grade 1 irAEs should be treated symptomatically and on an outpatient basis and do not need to interrupt ICI treatment while grade 2 or persistent grade 1 should consider oral corticosteroids (0.5-1mg/kg/day) and may need to temporary interrupt ICI treatment. Grade 3 and 4 are considered severe forms of presentation, with hospitalization needs and use of high-dose IV corticosteroids (1-2mg/kg/day). In grade 4 toxicities physicians must consider other immunosuppressive agents such as infliximab or micofenolate, permanent interrupt of ICIs and intensive care unit (ICU) admission. As grade 1-2 toxicities are usually seen and treated in the oncologist consultation, the emergency physicians normally encounter grade 3 and 4 toxicities. Eventhough these toxicities are infrequent, they are much more severe and their management, much more challenging. The most feared irAEs in the emergency room are pneumonitis, severe enterocolitis with colonic perforation, autoimmune type I diabetes mellitus presented as diabetic ketoacidosis, toxic epidermal necrolysis, miocarditis with reduced ejection fraction, encephalitis and myelitis.

We should not forget that emergency room is a stressful scenario where physicians must make difficult decisions, such as limit the treatment, decide the ceiling of care or indicate the ICU admission. So that, they must have the knowledge and the tools for early detection and management of the irAEs as much as advanced information related with the underlying cancer. They usually find problems with organizational constraints and disagreements between different specialists. A multidisciplinary approach should help to better attend these patients, with the emergency physician, the consulting oncologist and the organ-specific physician teams.

In conclusion, we should remember that early recognition and treatment of the irAEs can help to decrease the associated morbidity and mortality and also take into account that emergency physicians are seeing an increasing number of these irAEs and should have the knowledge and the tools to early recognize and treat them. We should not forget that risk is still present for weeks to months after termination of treatment and that multidisciplinary approach should be taken with these patients.

References

1 Hryniewicki AT, Wang C, Shatsky A et al. Management of immune checkpoint inhibitor toxicities: a review and clinical guideline for emergency physicians. Journal of Emergency Medicine 2018;55:489-502.

2 Haanen JB, Carbonnel F, Robert C et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Clinical Practice Guidelines. Annals of Oncology 2017; 28:119-142.

3 U.S. Departement of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), 4.03. Bethesda, MD: National Institutes of Health.

4 Puzanov I, Diab A, Abdallach K et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. Journal for Immunotherapy of Cancer 2017;5:95.

5 Brahmer J, Lacchetti C, Schneider B et al. Management of Immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714-1768

Immune-related adverse events in patients treated with immune chekpoint inhibitor therapy:

MANAGEMENT IN THE EMERGENCY ROOM

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HOT TOPICS

- Immune checkpoints inhibitors (ICIs) are becoming more commonly used among advanced-stage cancers
- The inhibition of IC may lead to unintended tissue damage which manifests into adverse effects that seem to arise from increase activity in the immune system
- Emergency physicians are encountering **increasing number of patients** on these medications as well as the associated side effects
- **Multidisciplinary** and **multi-organized** experts must agree and work together in the management and treatment of these patients

Table 1. List of Current ICIs and Their Indications*

Drug Class	Drug Name	Indications and Status	Most Common Toxicity of Any Grade (1–4)	Most Common High-Grade (3 or 4) Toxicity
CTLA-4 Inhibitor	Ipilimumab† (1)	Approved melanoma after surgery Late stage melanoma	Dermatologic (43.5%) Gastrointestinal (29.0%) Hepatic (3.8%) Endocrine (7.6%)	Gastrointestinal (7.6%)
	Tremelimumab (2)	Mesothelioma	Diarrhea (30–40%) Rash/pruritis (30–34%)	Diarrhea (5–10%)
PD-1 Inhibitor	Nivolumab (5)	Hodgkin's lymphoma HNSCC Advanced lung cancer Metastatic renal cell carcinoma Advanced melanoma High microsatellite instability tumors Merkel cell carcinoma	Dermatologic (29.1%) Gastrointestinal (11.2%) Endocrine (7.8%)	Hepatitis (2–3%)
	Pidilizumab	Under trial	NR	NR
	Pembrolizumab† (6)	Recurrent or metastatic HNSCC Metastatic NSCLC Advanced melanoma Renal cell carcinoma Merkel cell carcinoma	Dermatologic (10.7%) Gastrointestinal (8.1%) Endocrine (6.9%)	Pneumonitis (1.8%)
	Atezolizumab (2)	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors Merkel cell carcinoma Metastatic NSCLC Urothelial carcinoma	Diarrhea (18–20%)	Diarrhea (1–2%)
	Durvalumab (2)	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors Merkel cell carcinoma	Diarrhea (9–10%)	NR
	Avelumab	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors	NR	NR

ICI = immune checkpoint inhibitor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1/PD-2 = programmed death receptor-1 and -2; PD-L1 = programmed death-ligand 1; NR = not reported; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small-cell lung cancer.

* Current ICIs, their indications, most common associated toxicities reported as of December 2017.

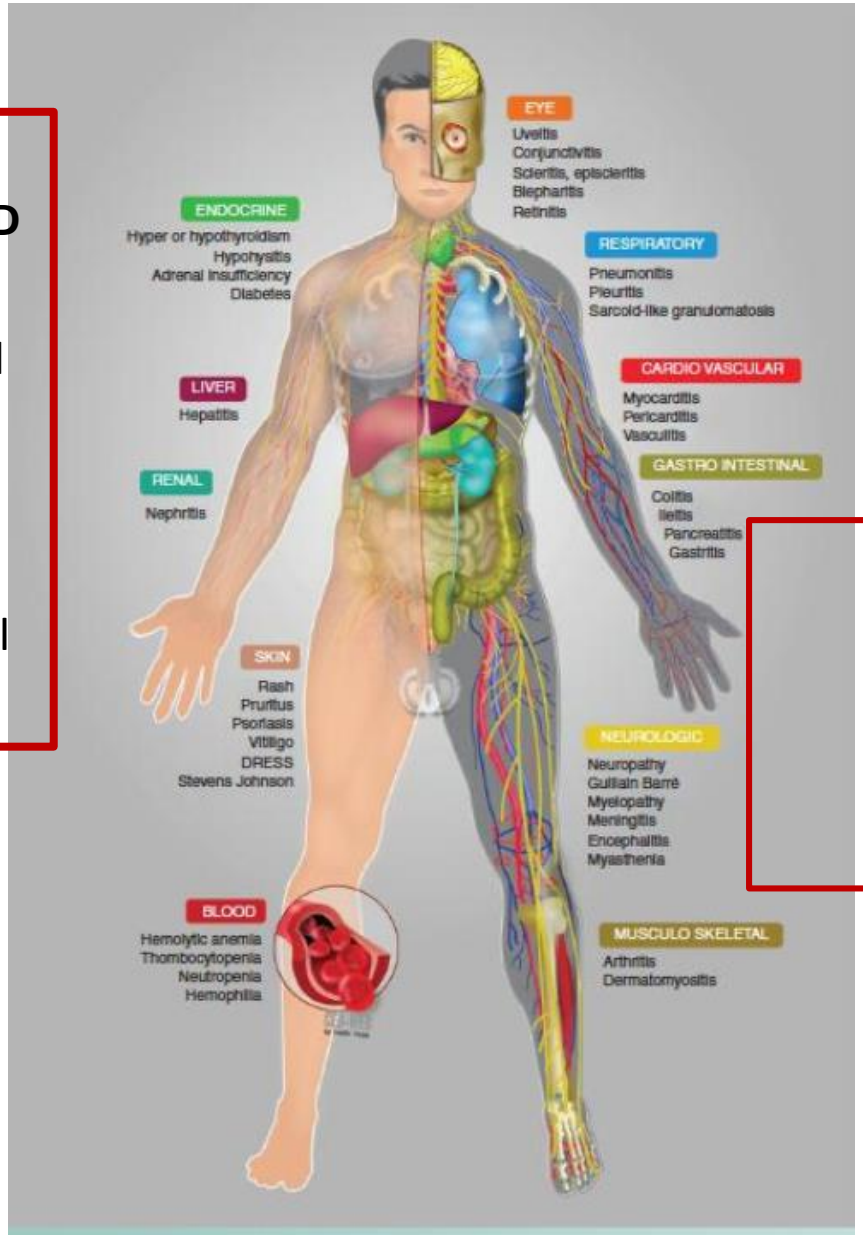
EMERGENCY ROOM:
THE ORDER WITHIN THE DISORDER

- Many patients with many pathologies
- Emergency physicians: what it is expected from us?
  - Differential diagnosis
  - Be aware of the different toxicities of immunotherapy
  - Early recognition of severe toxicities
  - Early treatment
- Contact with the oncologist +/- specialist if necessary

Immune-related adverse effects (irAEs)

FREQUENTLY REPORTED

- Dermatological
- Gastrointestinal
- Endocrine
- Pulmonary
- Rheumatologic
- Musculoskeletal



UNCOMMON

- Cardiovascular
- Neurological
- Renal
- Ophtalmological
- Hematological

Immune-Related AEs With Immunotherapy

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

Eye
- Uveitis
- Iritis

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

Hepatic
- Hepatitis, autoimmune

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

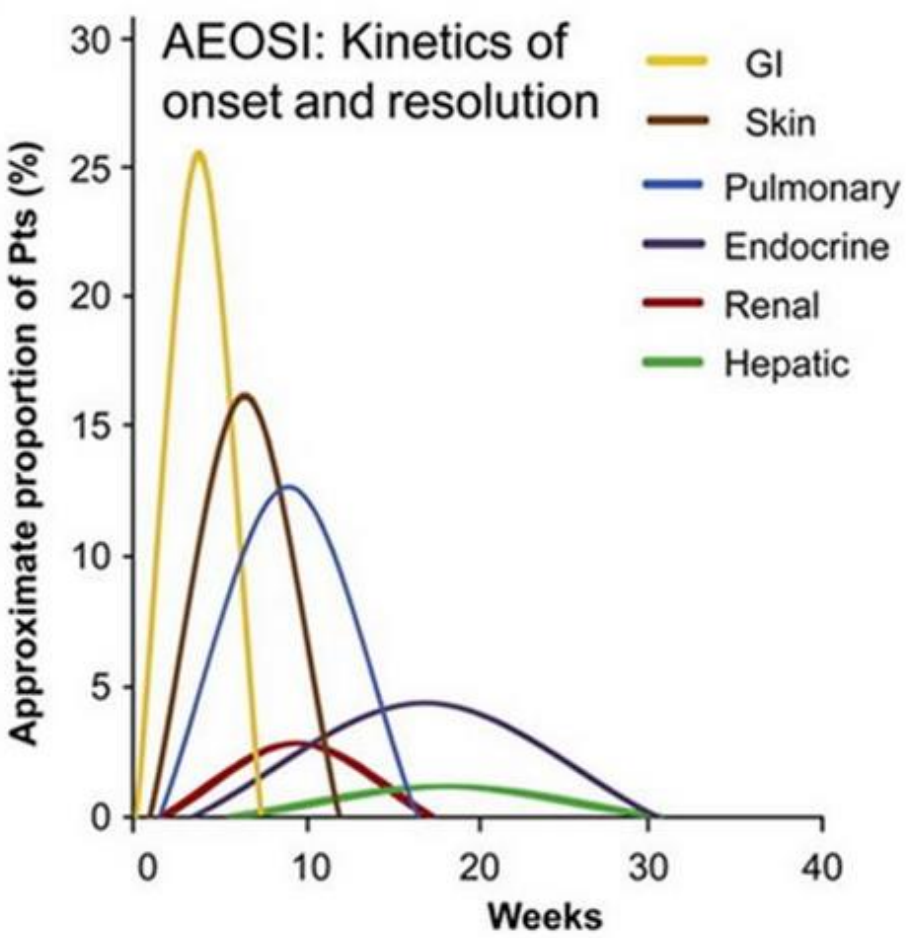
Gastrointestinal
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

Neurologic
- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barré
- Myasthenia gravis–like syndrome

Renal
- Nephritis, autoimmune
- Renal failure

If not vigilant, may result in more serious immune-related AEs

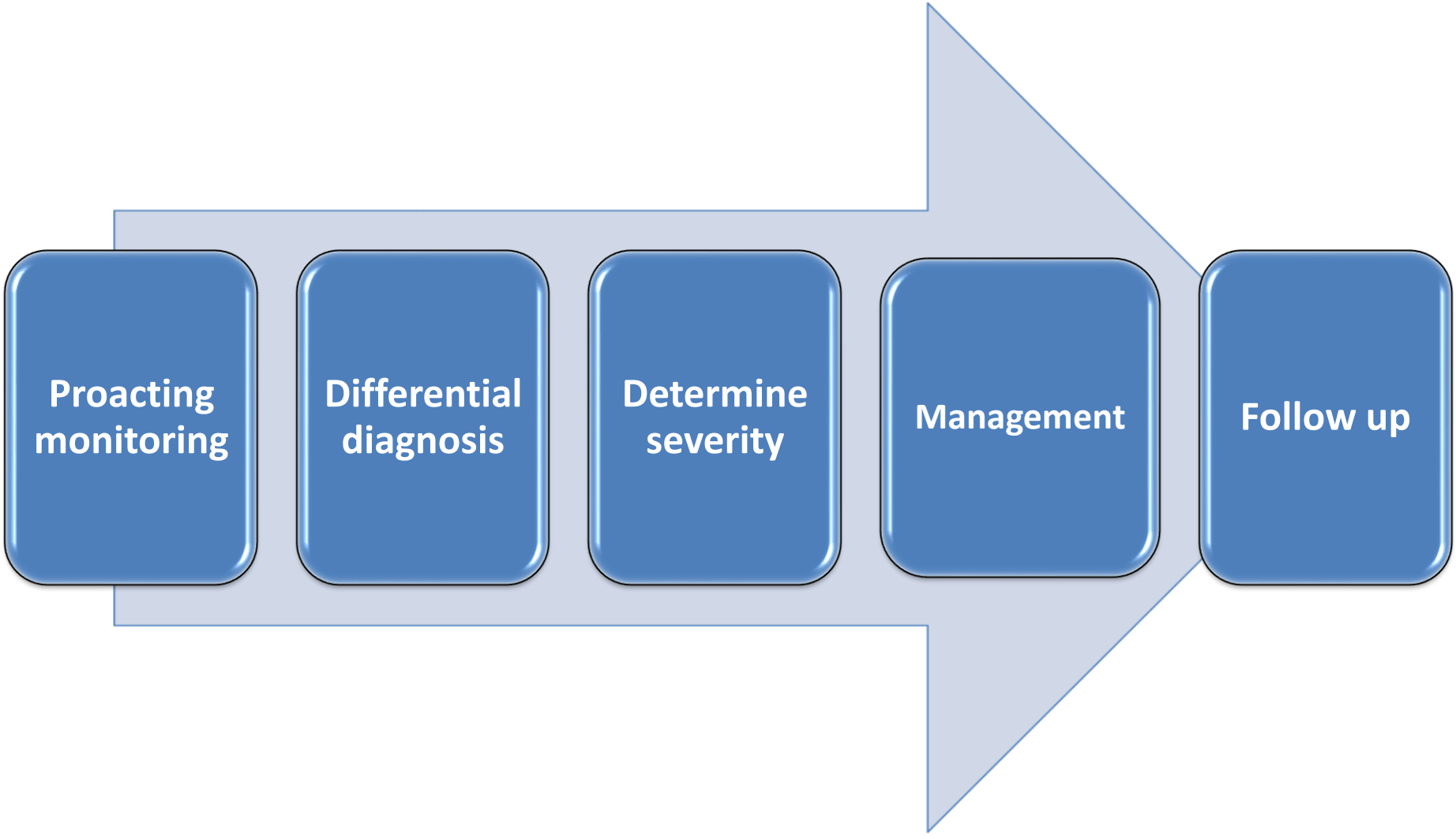
WHEN?: ARE WE ON THE +10 DAY?



TIMELINE OF irAEs:

- Quite early, mostly within weeks to 3 months
- Dermatological and GI typically manifest earlier
- Endocrine around 9 weeks
- Risk is still present for weeks to months after termination of treatment
- Recent history of ICI should keep irAEs on differential diagnosis

PRINCIPLE OF CLINICAL MANAGEMENT OF irAEs



DIFFERENTIAL DIAGNOSIS

- Pathology not related with the underlying cancer
- Complication of the underlying cancer
- Cancer progression
- Opportunistic infections: long term (>6 weeks) treatment with immunosupressive drugs increases the chance of opportunistic infections.
- irAEs affecting one system
- irAEs multisystem

DETERMINE SEVERITY AND MANAGEMENT

Grades of irAEs*	Management	Follow up
Grade 1 (mild)	Symptomatic treatment	Continue immunotherapy Ambulatory management
Grade 2 (moderate) **Persistent Grade 1**	Consider oral corticosteroids (0.5-1mg/kg/d)	Interrupt ICPi Ambulatory management
Grade 3 (severe)	High doses IV esteroids (1-2mg/kg/d)	Interrupt ICPi Hospitalization Specialist consult
Grade 4 (life-threatening)	- High doses IV esteroids (2mg/kg/d) - Consider other immunosupressive agents (infliximab/MMF)	Permanently interrupt ICPi Hospitalization Specialist consult Consider ICU admit

*Quantified using the Common Terminology Criteria for Adverse Events v4.03.

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

EMERGENCY ROOM: WHAT DO WE FIND?

CRITICAL PATIENTS
Grade 3-4 irAEs

irAEs most feared attended in the ER:

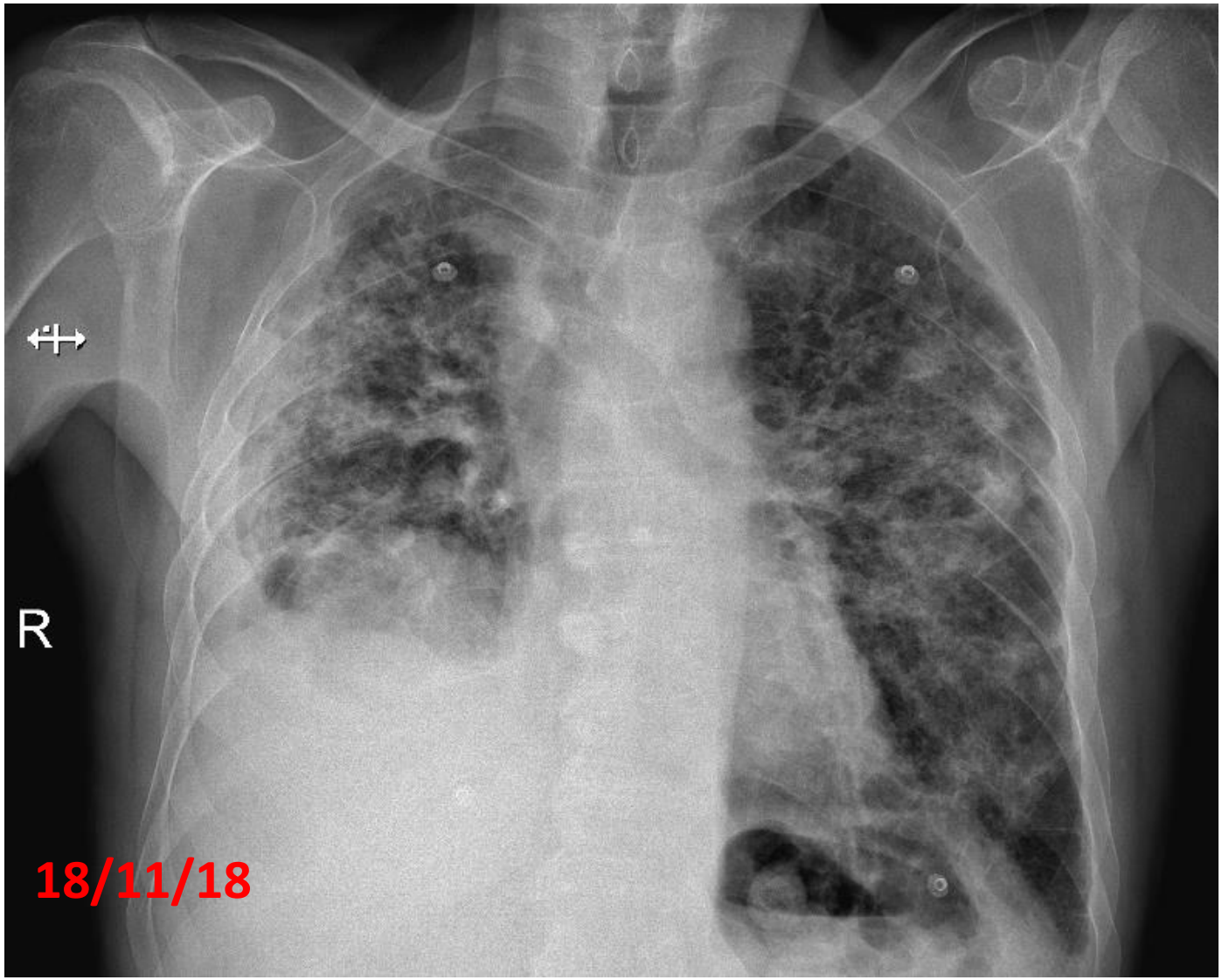
- Pulmonary toxicity: **pneumonitis**
- Gastrointestinal: severe enterocolitis +/- colonic perforation
- Endocrine: autoimmune type I diabetes mellitus presented as **diabetic ketoacidosis**
- *Skin*: **toxic epidermal necrolysis**
- Cardiac: **miocarditis** with reduced ejection fraction
- Neurological: **encephalitis, myelitis**

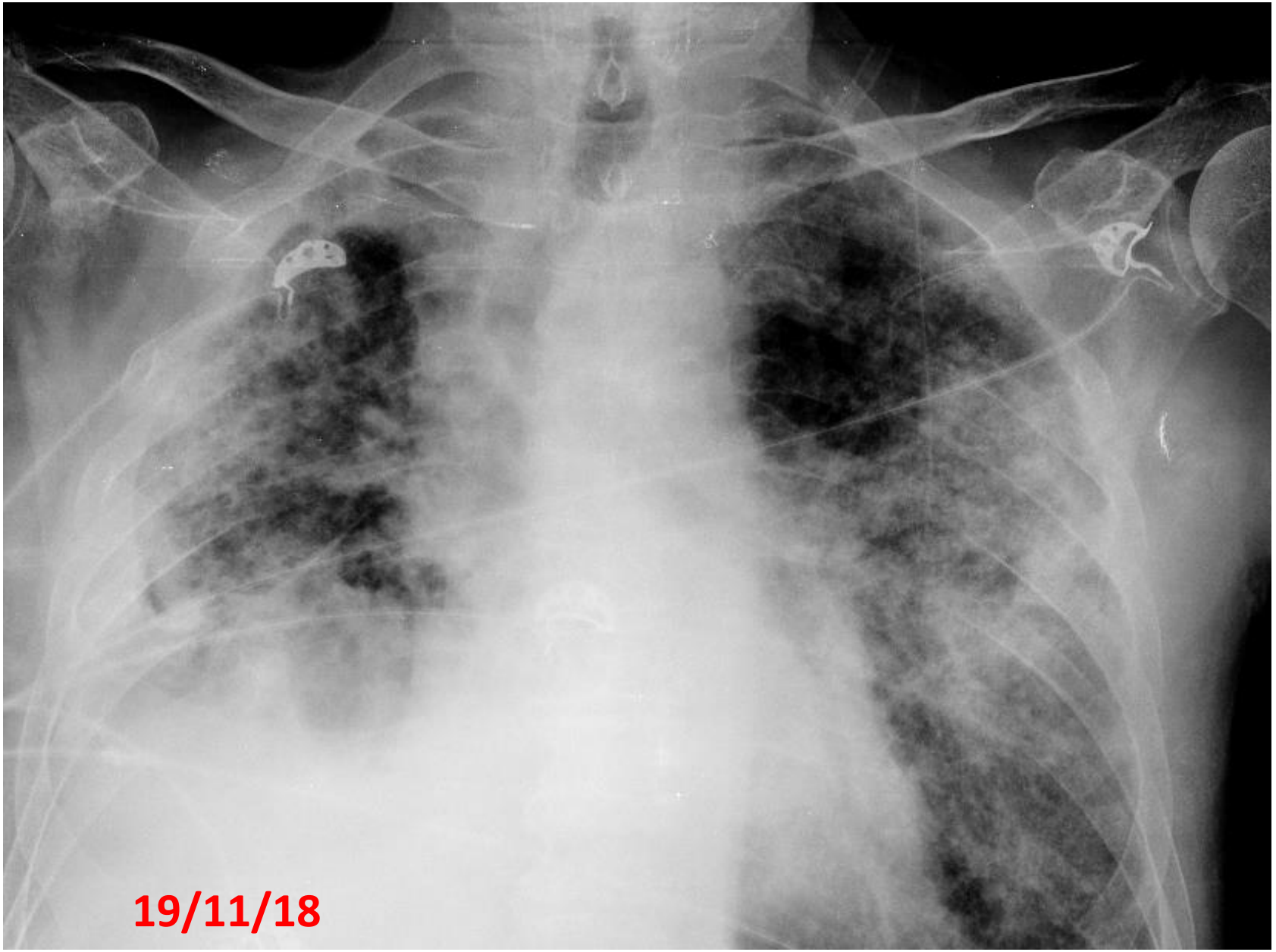
MAIN PROBLEMS AND NEEDS IN THE EMERGENCY ROOM

- **MAIN PROBLEMS**
  - Stressful scenario
  - Difficult decisions to make
  - Ceiling of care
  - Disagreements between specialists
  - Organizational constraints
  - Lack of advanced information of the underlying cancer

- **NEEDS TO DEVELOP**
  - Specifical training
  - Multidisciplinary approach: emergency physician, consulting oncologist and organ-specific physician
  - Semicritical units
  - “Pops-up”

Men, 66 years-old
Squamous cell lung cancer cT4N3M0 stage IIIB PDL1 80%
1L CDDP + VNR. Stop July 2018. Progression.
C1 Pembrolizumab 26/10/18

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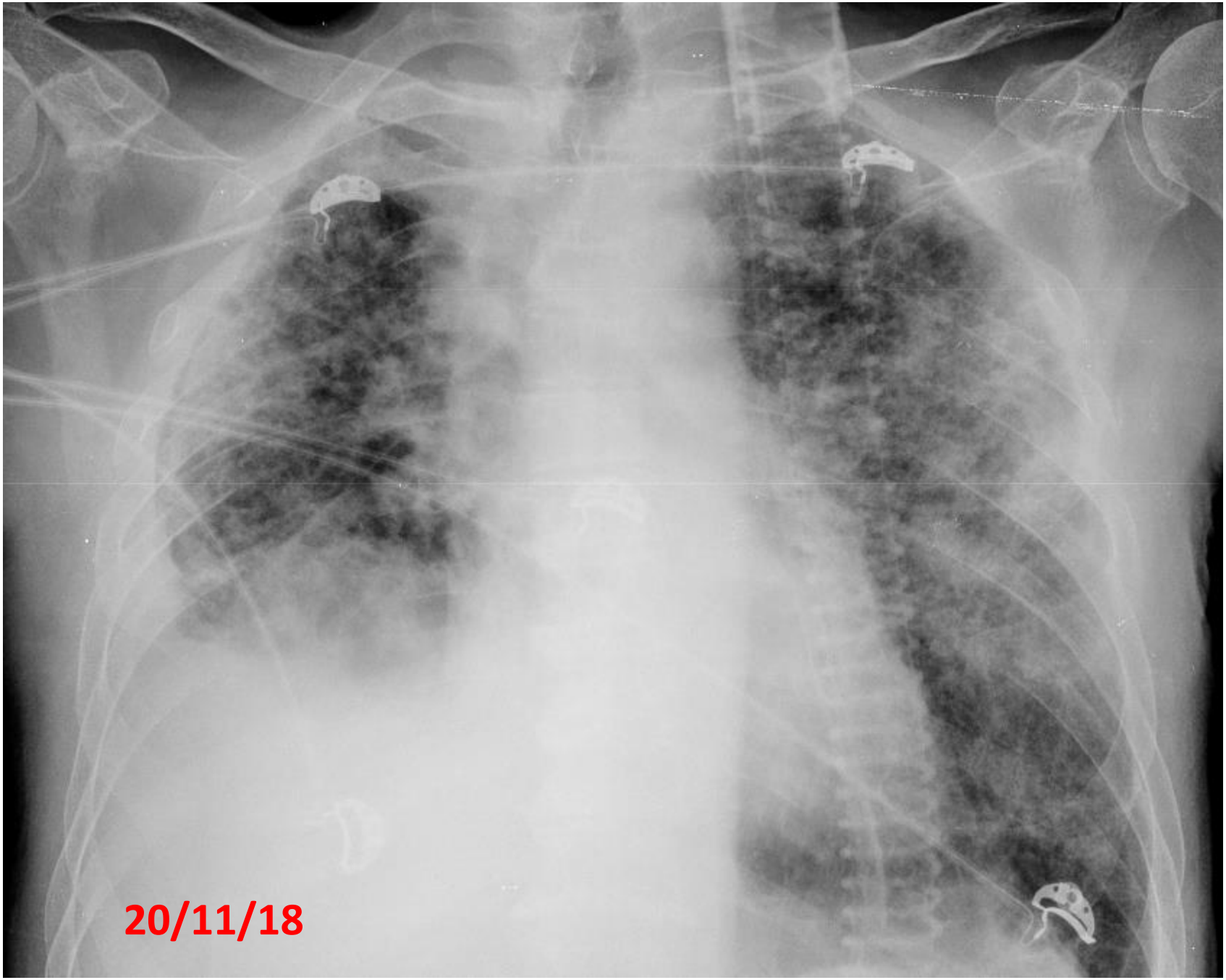
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PNEUMONITIS

- “Presence of new or progressive pulmonary infiltrates and ground glass changes on lung imaging studies”
- One of the most common causes of ICI-related death.
- DD: pneumonia, lymphangitic spread of disease, cancer progression, diffuse alveolar hemorrhage, acute pulmonary edema

- High doses of corticosteroids
- Infliximab or micofenolate if no improvement or worsening after 48 hours
- Cover with empiric antibiotic
- Consider *Pneumocystis* co-infection
- VMNI/high flow nasal oxygen
- Consider ICU admission

High-Flow Nasal Cannula Oxygenation in Immunocompromised Patients With Acute Hypoxemic Respiratory Failure: A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study

Virginie Lemiale, MD[1]; Matthieu Resche-Rigon, MD[2]; Djamel Mokart, MD[3]; Frédéric Pène, MD, PhD[4]; Laurent Argaud, MD[5]; Julien Mayaux, MD[6]; Christophe Guitton, MD[7]; Antoine Rabbat, MD[8]; Christophe Girault, MD, PhD[9]; Achille Kouatchet, MD[10]; François Vincent, MD[11]; Fabrice Bruneel, MD[12] Martine Nyunga, MD[13]; Amélie Seguin, MD[14]; Kada Klouche, MD[15]; Gwenahel Colin, MD[16]; Loay Kontar[17], Pierre Perez, MD[18]; Anne-Pascale Meert, MD, PhD[19], Dominique D. Benoit, MD, PhD[20]; Laurent Papazian, MD, PhD[21,22], Alexandre Demoule, MD, PhD[6]; Sylvie Chevret, MD, PhD[2]; Elie Azoulay, MD, PhD[1]

CONCLUSIONS: in immunocompromised patients with hypoxemic acute respiratory failure, High-flow nasal oxygen when compared with standard oxygen did not reduce intubation or survival rates.

Crit Care Med. 2017 Mar;45(3J):e274-e280. doi: 10.1097/CCM.0000000000002085

CONCLUSIONS

- ✓ Early recognition and treatment of the irAEs can help to decrease the associated morbidity and mortality
- ✓ Emergency physicians are seeing an increasing number of these irAEs and should have the knowledge to early recognize and treat them
- ✓ Include irAEs in the differential diagnosis when appropriate
- ✓ Risk is still present for weeks to months after termination of treatment
- ✓ Multidisciplinary approach should be taken with these patients

Thank you!