Potential Competing Interests: The authors report no competing interests.

1. Kantrowitz A, Tjonneland S, Freed PS, Phillips SJ, Butner AN, Sherman JL Jr. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA*. 1968;203(2):113-118.
2. McBride LR, Miller LW, Naunheim KS, Pennington DG. Axillary artery insertion of an intra-aortic balloon pump. *Ann Thorac Surg*. 1989;48(6):874-875.
3. Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Axillary artery: an alternative site of arterial cannulation for patients with extensive aortic and peripheral vascular disease. *J Thorac Cardiovasc Surg*. 1995;109(5):885-890.
4. Estep JD, Cordero-Reyes AM, Bhimaraj A, et al. Percutaneous placement of an intra-aortic balloon pump in the left axillary/subclavian position provides safe, ambulatory long-term support as bridge to heart transplantation. *JACC Heart Fail*. 2013;1(5):382-388.
5. Umakanthan R, Hoff SJ, Solenkova N, et al. Benefits of ambulatory axillary intra-aortic balloon pump for circulatory support as bridge to heart transplant. *J Thorac Cardiovasc Surg*. 2012;143(5):1193-1197.
6. Barnett MG, Swartz MT, Peterson GJ, et al. Vascular complications from intraaortic balloons: risk analysis. *J Vasc Surg*. 1994;19(1):81-87.
7. Freed PS, Wasfie T, Zado B, Kantrowitz A. Intra-aortic balloon pumping for prolonged circulatory support. *Am J Cardiol*. 1988;61(8):554-557.

https://doi.org/10.1016/j.mayocp.2018.01.010

Multiple Cranial Neuropathies From Nivolumab in a Patient With Metastatic Hepatocellular Carcinoma

To the Editor: Nivolumab is a checkpoint inhibitor immunotherapy with multiple clinical indications. Based on encouraging activity from a phase 1/2 single-arm study,[1] nivolumab now has accelerated approval for use as second-line therapy for advanced hepatocellular carcinoma.[2] A phase 3 confirmatory study comparing nivolumab with sorafenib is ongoing.[3] As the use of nivolumab increases, it is important to be aware of potential immune-related adverse effects, including the rare subset of neurotoxicities. To date, nivolumab has been linked to cases of encephalitis, acute and chronic immune demyelinating polyneuropathy, myasthenic syndromes, and myositis.[4] We report a case of nivolumab-induced multiple cranial neuropathies.

Report of Case. Our patient, a 64-year-old man with a history of metastatic hepatocellular carcinoma from hepatitis C, was treated with off-label nivolumab, 3 mg/kg, every 2 weeks.[1] There had been progression of disease despite various therapies, including transarterial chemoembolization, sorafenib, and a blinded study medication as part of a placebo-controlled trial evaluating tivantinib.[5] After receiving 4 doses of nivolumab, the patient gradually developed slurred speech, difficulty swallowing, abnormal extraocular movements, and left-sided facial droop over the course of a few weeks. He had lost 6.75 kg. At this point, he was treated empirically with dexamethasone, 20 mg/d, for a potential drug adverse effect and had a percutaneous endoscopic gastrostomy tube placed for enteral nutrition.

Two weeks later, the patient had worsening of symptoms, with severe bilateral facial droop, bilateral internuclear ophthalmoplegia, left-sided ptosis, severe dysarthria, and an impaired gag reflex, consistent with dysfunction in bilateral cranial nerves III, VII, X, and XII. He was hospitalized and intubated shortly thereafter due to inability to protect his airway. Lumbar puncture specimens yielded negative results on cytologic examination, comprehensive infectious studies, and paraneoplastic antibody tests. Magnetic resonance imaging of the brain with contrast medium revealed faint enhancement of left cranial nerve III consistent with inflammation (Figure).

The patient was diagnosed with nivolumab-induced multiple cranial neuropathies. He was treated with simultaneous intravenous methylprednisolone, 1 g/d for 5 days, and plasma exchange for 7 days. On hospital day 8, he was extubated and had improvement in extraocular movements. Because of persistent left-sided facial droop, dysarthria, and dysphagia, he was also treated with a 5-day course of intravenous immunoglobulin, 2 g/kg daily. Four months after hospitalization, he had nearly complete recovery with his only deficits being a mild left-sided facial droop and left

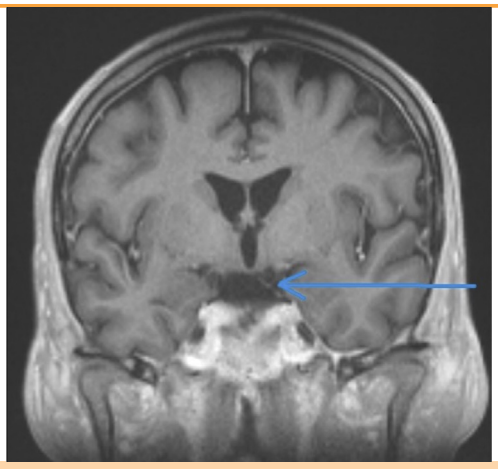

FIGURE. Coronal T1-weighted magnetic resonance imaging of the brain with contrast medium shows enhancement of left cranial nerve III (arrow).

hemifacial spasm. The dysphagia, dysarthria, and ptosis had fully resolved, and his percutaneous endoscopic gastrostomy tube was removed.

Discussion. Despite the rarity of neurotoxicity secondary to checkpoint inhibitor therapies, it must be considered in all patients with previous exposure who present with a new neurologic deficit. Immune-related neurotoxicity remains a diagnosis of exclusion; it requires ruling out brain metastases, infection, and paraneoplastic syndromes. However, a timely diagnosis is crucial. As illustrated by our case, nivolumab-induced neurotoxicity can be both life-threatening and reversible with the appropriate treatment. Although the exact mechanism of nivolumab-induced cranial neuropathy is unknown, this case suggests that treatment with corticosteroids alone may be insufficient, at least in severe cases, and that the addition of plasmapheresis and intravenous immunoglobulin can lead to sustained recovery.

Caroline H. Siegel, MD
Richard S. Finn, MD
Michael G. Ho, MD
University of California
Los Angeles, CA

1. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017. 2017;389(10088):2492-2502.
2. US Food and Drug Administration. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib [news release]. US Food and Drug Administration website. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577166.htm. Updated September 25, 2017. Accessed October 24, 2017.
3. Bristol-Myers Squibb. A Randomized, Multi-center Phase III Study of Nivolumab Versus Sorafenib as First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma (CheckMate 459: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 459). ClinicalTrials.gov Identifier: NCT02576509. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02576509. Accessed October 24, 2017.
4. Touat M, Talmasov D, Ricard D, Psimaras D. Neurological toxicities associated with immune-checkpoint inhibitors. *Curr Opin Neurol*. 2017; 30(6):659-668.
5. Daiichi Sankyo, Inc. A Phase 3, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects With MET Diagnostic-High Inoperable Hepatocellular Carcinoma Treated With One Prior Systemic Therapy. ClinicalTrials.gov Identifier: NCT0175576. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01755767. Accessed November 20, 2017.

https://doi.org/10.1016/j.mayocp.2018.01.001

Statin Use Associated With a Decreased Risk of Community-Acquired *Staphylococcus aureus* Bacteremia

To the Editor: We read with great interest the recent article by Smit et al[1] on statin use associated with a decreased risk of community-acquired *Staphylococcus aureus* bacteremia (CA-SAB), particularly in patients with chronic kidney disease and patients with diabetes. They explained that these results were unlikely due to direct antimicrobial effects of statins on *S aureus* but more likely due to the pleiotropic effects of statins reducing important isoprenoid intermediates, resulting in decreased bacterial invasion and inducing neutrophil extracellular traps.

By reviewing the available literature of statins' in vitro antibacterial effects, we observed that simvastatin, followed by atorvastatin, generally exerted the greatest direct antibacterial effect (lowest minimum inhibitory concentration) against *S aureus* compared with other statins.[2] This finding supports the view that direct antimicrobial effects were unlikely responsible for statins' protective effects because Smit et al have provided complementary evidence that the risk of contracting CA-SAB was higher, rather than lower, in patients taking simvastatin or atorvastatin compared with the other statins.[1] As such, it is more probable that statins reduce CA-SAB risk through other host-related mechanisms.

Interestingly, a recent study by Plotkin and Konakieva[3] found that steroid hormones with the 3-hydroxy moiety (eg, cholesterol and estradiol) increased carotenoid levels in *S aureus*, which potentially increases bacterial virulence.[4] Patients with chronic kidney disease usually have low levels of sex steroid hormones,[5] but high levels of estradiol may present in septic patients.[6] Knowledge of the antibiotic treatment outcomes for patients with chronic kidney who have CA-SAB and are statin users, compared with nonusers, might provide clues as to whether statins could offer additional benefits by suppressing the antagonistic precursor cholesterol molecule and downstream steroidal hormones sufficiently, resulting in efficacious antibiotic therapy.

Because statins may induce new-onset diabetes and the colonization of skin and mucosae with *S aureus* predisposes diabetic patients to infections,[7,8] statin users with diabetes might be expected to have a higher risk of CA-SAB. However, the results of Smit et al[1] revealed otherwise. Other conflicts yet to be reconciled include opposing evidence that statins do not produce neutrophil extracellular trap production[9] or why meta-analysis of clinical trials examining the outcome of statins in septic patients differ.[10,11] In addition, when statins influence the human gut microbiota[12] or activate nuclear receptors,[13] the resultant impact to the human immune system has not been elucidated.

The work of Smit et al is interesting and timely and should stimulate further investigation into the role of statins in preventing bacteremia.

Humphrey H.T. Ko, BSc(Pharm)(Hons)
Ricky R. Lareu, BSc (Hons), MMedSci, GradDipEd, PhD
Brett R. Dix, BSc(Hons), PhD
Jeffery D. Hughes, BPharm, GradDipPharm, MPharm, PhD
Curtin University
Perth, Western Australia, Australia

1. Smit J, López-Cortés LE, Thomsen RW, et al. Statin use and risk of community-acquired *Staphylococcus aureus* bacteremia: a population-based