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Dexmedetomidine-Associated Hyperpyrexia in Three Critically Ill Patients With Coronavirus Disease 2019

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Objectives: To present three patients with severe coronavirus disease 2019 infection who developed life-threatening hyperpyrexia while being treated with dexmedetomidine for sedation.

Data Sources: Clinical records.

Study Selection: Case report.

Data Extraction: Relevant clinical information.

Data Synthesis: We describe three patients, a 60-year-old female, 43-year-old female, and 46-year-old male, who were hospitalized in surge ICUs during the coronavirus disease 2019 pandemic in the early spring of 2020. All developed hyperpyrexia, defined as a temperature above 41.1°C, following an increase in dexmedetomidine dosing to above 1.5 µg/kg/hr. Fevers resolved following discontinuation of dexmedetomidine.

Conclusions: While the exact mechanism of hyperpyrexia remains unclear, findings in this study suggest that high doses of dexmedetomidine infusion are associated with hyperpyrexia in a seemingly dose-dependent fashion in critically ill patients with coronavirus disease 2019. Coronavirus disease 2019 infection causes a hyperinflammatory state characterized by pro-inflammatory cytokine dysregulation. Dexmedetomidine, a centrally acting alpha-2 agonist, may alter hypothalamic temperature regulation through disturbances in neurotransmitter expression and metabolism. We postulate that the use of high-dose dexmedetomidine in a hyperinflammatory state may increase the risk of developing hyperpyrexia in this severe disease state.

Key Words: coronavirus disease 2019; COVID-19; dexmedetomidine; hyperpyrexia; severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 causing coronavirus disease 2019 (COVID-19) has led to increased admissions to ICUs (1, 2). Given the risk of aerosolization associated with noninvasive ventilation, thresholds for intubation with rapid sequence induction are low (3). Sedation for the mechanically ventilated patient is critical to prevent unintentional extubation and promote patient comfort; however, the optimal agent for primary sedation is debated (4). Dexmedetomidine, a highly selective, centrally acting alpha-2 adrenergic receptor agonist, is a preferred agent, as it has analgesic effects without respiratory depression (5–7). In randomized controlled studies comparing dexmedetomidine with midazolam and propofol, dexmedetomidine was associated with shorter ICU admissions and time to extubation (8–10).

However, since 2015, multiple observational studies have been published highlighting the temporal association between dexmedetomidine infusion and hyperthermia with temperatures above 39°C (11–15). The following case series is unique from the previously reported studies in that all three of our patients experienced hyperpyrexia, which is distinct from hyperthermia and is defined by an increased body temperature above 41.1°C (16). Hyperpyrexia is a pathologic condition that results in abnormal elevation of the hypothalamic thermoregulatory set point, while hyperthermia is secondary to decreased heat loss or increased heat production leading to elevated body temperature above the normal thermoregulatory set point (17). Hyperpyrexia in the critically ill patient is of great clinical significance because it may result in cell death and local damaging effects that include extravasation and vascular stasis (18).

Retrospective analysis reveals that hyperpyrexia developed following temporally associated increases in dexmedetomidine dosing and resolved following discontinuation of the medication. This association warrants attention amidst the current COVID-19 pandemic, as providers not familiar with the potential for

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dexmedetomidine drug fever are called to the frontlines to participate in ICU-level care. Furthermore, hyperpyrexia that complicates COVID-19 disease in an already vulnerable population could result in increased mortality and morbidity (19, 20).

CASE REPORT

We describe three patients who were hospitalized in surge ICUs during the COVID-19 pandemic in the early spring of 2020. Informed consent for publication was obtained for all patients described. All patients were managed under the care of an adult-medicine trained intensivist. All three patients presented similarly with prodromal viral symptoms and ultimately required intubation for acute hypoxemic respiratory failure secondary to acute respiratory distress syndrome (ARDS) and COVID-19. A review of laboratory data at the time of hyperpyrexia is available in **Table 1**.

Patient 1 was a 60-year-old female with a history of hypertension, type 2 diabetes mellitus (DM2), class II obesity (body mass index [BMI] 35), latent tuberculosis, hypothyroidism, cerebrovascular accident, panic disorder, and fibromyalgia. Prior to admission medications included ranitidine, metformin, levothyroxine, latanoprost, gabapentin, duloxetine, dicyclomine, and calcium carbonate.

She was endotracheally intubated on day 12 of illness and initially sedated with hydromorphone and propofol. On day 14, propofol was discontinued due to increased serum triglycerides and dexmedetomidine was titrated to 1.5 µg/kg/hr over 1 hour. Fever developed 24 hours later, increasing over 8 hours to a maximum of 42.4°C at approximately 32 hours of infusion (**Fig. 1A**). The dexmedetomidine infusion was promptly discontinued and aggressive external cooling measures (including use of an Arctic Sun Temperature Management System [Medivance, Louisville, CO] and application of ice packs

to the groin, axilla, and neck) were performed; however, her body temperature remained above 39°C for 7 hours. Follow-up laboratory studies were notable for a new increase in C-reactive protein to 367 mg/L (reference range < 8.0 mg/L), ferritin to 3,653 ng/mL (reference range, female: 10–200 ng/mL), and lactate to 3.9 mmol/L (reference range, 0.5–2.2 mmol/L). Interleukin (IL)-6 was also markedly increased to 428 pg/mL (reference range ≤ 1.8 pg/mL). Using the Naranjo algorithm for adverse drug reaction (ADR) and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality categories, she had a “probable” reaction (21, 22).

In the 24 to 48 hours following hyperpyrexia, the patient developed cardiovascular failure requiring increasing inotrope and vasopressor support, as well as oliguric renal failure, metabolic acidosis refractory to continuous renal replacement therapy, and fixed and dilated pupils consistent with irreversible brain injury, with intracerebral hemorrhage ruled out by CT scan. Based on her poor prognosis, her family elected for comfort care and she died shortly after discontinuing vasoactive medications.

Patient 2 was a 43-year-old female with a history of hypertension, mild intermittent asthma, hyperlipidemia, and class I obesity (BMI 33). Home medications included amlodipine and albuterol, which she was not regularly using. She presented to care following 1 week of subjective fevers and cough, and she was endotracheally intubated on hospital day 2. She was initially sedated with propofol and hydromorphone. In the following days, dexmedetomidine was begun at a dose of 0.2 µg/kg/hr and steadily increased to a dose of 2 µg/kg/hr over a 6-hour period. During this time, the patient developed a new fever to 38.6°C that decreased once she reached a steady infusion dose of 2 µg/kg/hr. She developed new fever to a maximum of 42°C at approximately 72 hours after the beginning of the 2 µg/kg/hr dexmedetomidine infusion, on day 16 of illness

TABLE 1. Patient Clinical and Laboratory Data at Time of Maximum Body Temperature

Clinical Data	Patient 1	Patient 2	Patient 3
Age/sex	60/female	43/female	46/male
Comorbidities	DM2, latent tuberculosis, hypertension, cerebrovascular accident, hypothyroidism, and class II obesity	Hypertension, hyperlipidemia, reactive airway disease, and class I obesity	DM2 and hyperlipidemia
Day of illness at peak temperature	14	15	13
Dexmedetomidine dose (µg/kg/hr)	1.5	2.0	2.0
WBC (K/µL)	6.71↓	10.9↑	5.98↔
Lymphocyte count (K/µL)	1.96↑	0.86↑	4.4↔
Lactate dehydrogenase (U/L)	NA	435↑	646↔
D-dimer (ng/mL)	> 10,000↑	4,219↑	3,016↓
C-reactive protein (mg/L)	193.8↓	275.5↑	291.5↑
Erythrocyte sedimentation rate (mm/hr)	115↑	88↔	89↑
Ferritin (µg/L)	3,653↑	533↑	1,333↓
Creatine kinase (U/L)	879↑	43↓	254↓
Troponin T (ng/L)	131↑	NA	17↑

DM2 = type 2 diabetes mellitus, NA = not available.

Laboratory trends compared to the prior day are represented by arrows.

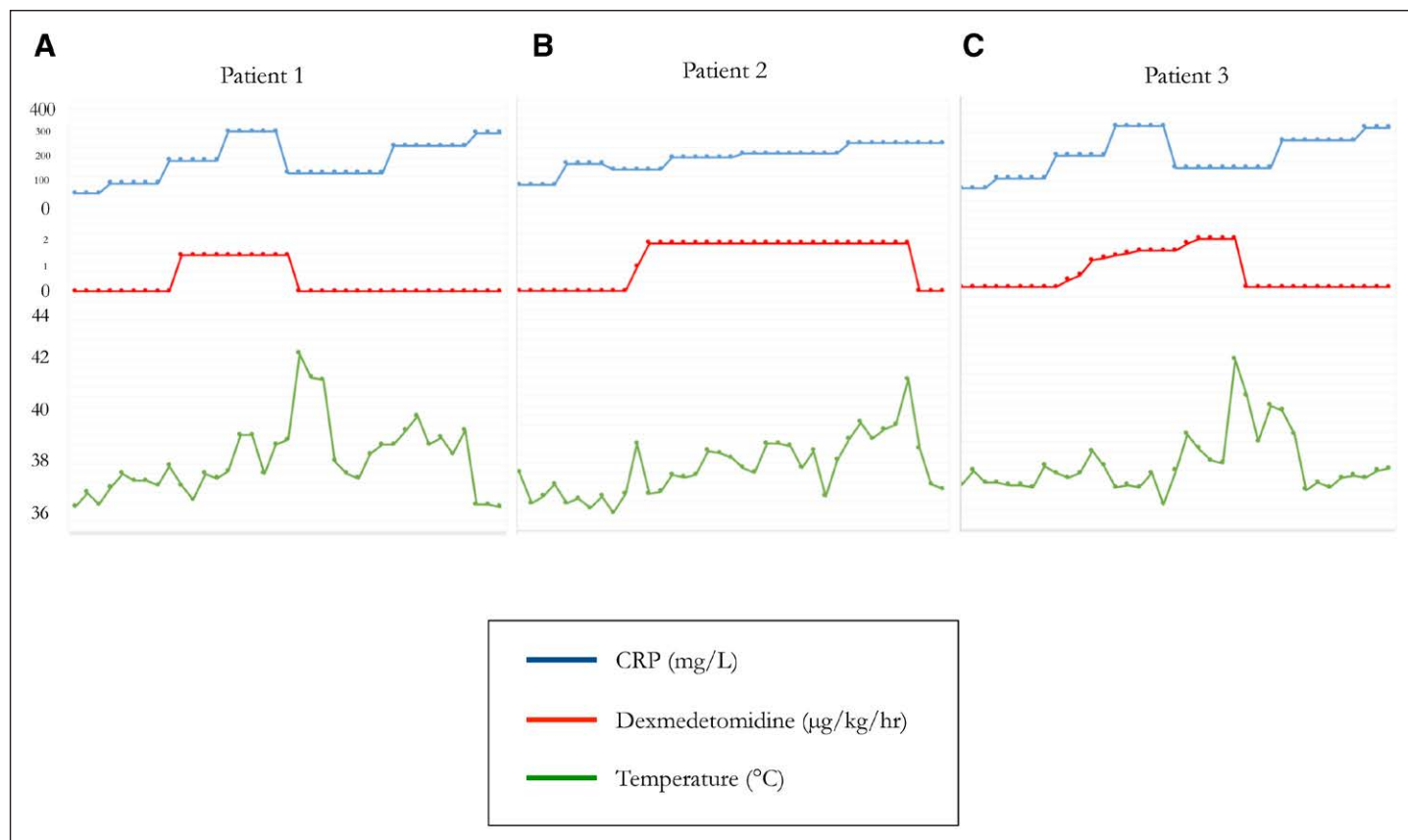


Figure 1. The figure illustrates the temporal relationship between dexmedetomidine dose increase and subsequent body temperature elevation. C-reactive protein (CRP) levels (mg/L), dexmedetomidine dose ($\mu\text{g}/\text{kg}/\text{hr}$), and temperature ($^{\circ}\text{C}$) for each patient in the days around maximum temperature (**A**) patient 1, (**B**) patient 2, and (**C**) patient 3.

(**Fig. 1B**). Serum IL-6 at this time was 7.3 pg/mL (reference range ≤ 1.8 pg/mL). The dexmedetomidine infusion was promptly discontinued and the patient was successfully cooled with aggressive external cooling techniques, which included use of an Arctic Sun Temperature Management System and application of ice packs to the groin, axilla, and neck. Her body temperature returned to 37.2°C for 4 hours after coming off the dexmedetomidine drip. One week later, she was rechallenged with dexmedetomidine periextubation at a dose of $0.5 \mu\text{g}/\text{kg}/\text{hr}$ and again developed fever to 39.6°C beginning 3 hours after dexmedetomidine infusion. Despite discontinuation of the medication, the fevers persisted for a 24-hour period and were associated with nontraumatic rhabdomyolysis with creatinine kinase reaching a peak of 33,535 U/L (reference range, female: 40–150 U/L). Her body temperature gradually returned to 37°C over the next 24 hours. Fortunately, the patient did not show evidence of acute kidney injury and the rhabdomyolysis improved with IV hydration. Using the Naranjo algorithm for ADR and the WHO-UMC causality categories, she had a “probable” event (21, 22). Patient 2 has since returned to her home, but she continues with outpatient home health therapies to address her critical illness myopathy associated with her prolonged hospitalization with COVID-19.

Patient 3 was a 46-year-old male with a history of DM2 and hyperlipidemia. His home medications included atorvastatin, empagliflozin, flaxseed, metformin, and multivitamin. He presented to care following 5 days of cough, congestion, and fever with temperatures ranging between 38.9°C and 39.4°C . He was

endotracheally intubated upon arrival to the hospital (day 7 of illness) and was initially sedated with propofol and hydromorphone. In preparation for extubation on hospital day 5, dexmedetomidine was initiated at a dose of $0.3 \mu\text{g}/\text{kg}/\text{hr}$ and gradually increased over the subsequent 24 hours to $1.5 \mu\text{g}/\text{kg}/\text{hr}$ without any sustained increases in body temperature. As depicted in **Figure 1C**, the patient developed fever to 38.7°C once the dexmedetomidine was increased to $1 \mu\text{g}/\text{kg}/\text{hr}$, but body temperature returned to normal over the next 3 hours. The dose of dexmedetomidine was maintained at $1.5 \mu\text{g}/\text{kg}/\text{hr}$ for the subsequent 12 hours without any associated fevers. With the next dose increase to $1.6 \mu\text{g}/\text{kg}/\text{hr}$, body temperature increased within 1 hour to 38.9°C and remained increased over the following 24 hours reaching a peak of 42°C associated with incremental dose increases of dexmedetomidine to a maximum of $2 \mu\text{g}/\text{kg}/\text{hr}$ (**Fig. 1C**). Dexmedetomidine was discontinued and his body temperature returned to 37.2°C over the next 12 hours. His IL-6 at this time was 21.4 pg/mL (normal reference range: 0–15.5 pg/mL), down from 184 pg/mL at admission.

About 2 weeks later, the patient was briefly rechallenged on dexmedetomidine at a dose of $0.3 \mu\text{g}/\text{kg}/\text{hr}$ for acute agitation with no associated fever over an 8-hour period of use. He had a “possible” ADR by the Naranjo algorithm and a “probable” event by the WHO-UMC causality categories (21, 22). Patient 3 has since been extubated but suffers from critical illness myopathy and polyneuropathy. He continues his recovery in a rehabilitation hospital.

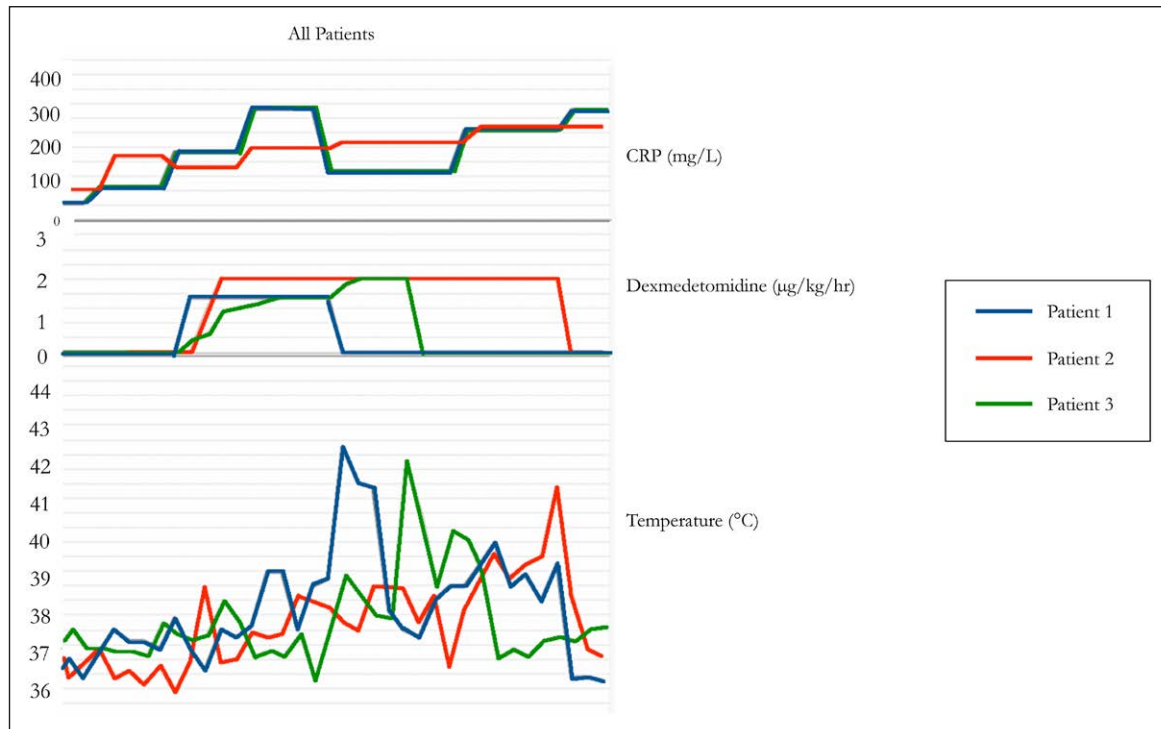


Figure 2. C-reactive protein (CRP) levels (mg/L), dexmedetomidine dose ($\mu\text{g}/\text{kg}/\text{hr}$), and temperature ($^{\circ}\text{C}$) for all patients in the days around maximum temperature.

DISCUSSION

This case series offers support for the association between high-dose dexmedetomidine infusions and hyperpyrexia in a subpopulation of critically ill COVID-19 patients. Findings collated in **Figure 2** demonstrate that all episodes of hyperpyrexia, defined as a temperature above 41.1°C , were preceded by an increase in dexmedetomidine dosing to $1.5 \mu\text{g}/\text{kg}/\text{hr}$ or above. High doses of dexmedetomidine infusion are potentially linked to the isolated episodes of hyperpyrexia in this cohort. While fever is common in the COVID-19 population requiring ICU admission (23, 24), reports of hyperpyrexia are less common (20) in contrast to the three aforementioned cases of patients with COVID-19 on high doses of dexmedetomidine. The natural course of fever in the COVID-19 patient population is not well-described in the current literature. A cohort study from patients in Wuhan, China (25), reported the occurrence rate of fever in 100% of ICU patients with the majority of these patients (54%) having body temperatures between 38.1°C and 39°C (26). In our experience, adult patients with COVID-induced ARDS typically demonstrate cyclic fevers lasting up to 24 hours or more at least every few days in the ICU setting.

Preceding dexmedetomidine up-titration, there was no concern for the development of new infection with no trends toward leukocytosis, worsening respiratory distress, or newly positive blood or respiratory cultures in these patients. Additionally, none of the patients had received dopamine D2 receptor antagonists at the time of hyperpyrexia development. This is important to consider as dopamine antagonists are commonly implicated in neuroleptic malignant syndrome, which can present with dystonia and high body temperatures. Two patients had “probable” ADRs and one had a “possible” ADR by the Naranjo ADR scale, a validated probability scale used to assess relationship-likelihood of

suspected ADRs (21), and all three had “probable” ADRs by the WHO-UMC causality categories (22).

Although the mechanism is uncertain, doses of greater than $1 \mu\text{g}/\text{kg}/\text{hr}$ have been associated with probable ADRs in prior case series (13). It is postulated that centrally acting alpha-2 agonists such as dexmedetomidine alter the expression of noradrenaline, serotonin, and dopamine, the neurotransmitters that mediate hypothalamic regulation of temperature (12). In animal studies, alpha-2 agonists block the activation of thermogenic premotor neurons, thereby decreasing body temperature. In mouse models of alpha-2 receptor knockout, this temperature decrease is not observed; it is therefore possible that polymorphisms in these receptors resulting in decreased receptor activity may predispose patients to hyperthermic reactions (27). Alternatively, dexmedetomidine may induce hyperthermia through dopaminergic blockade such as that associated with neuroleptic malignant syndrome (12). Other animal models have demonstrated that under different environmental conditions, alpha agonists result in hyperthermia, suggesting that changes in metabolism of neurotransmitters may also be mediated by other unknown external factors (27). It is possible, therefore, that an interaction between high-dose alpha agonists and COVID-19 may predispose to hyperpyrexia. More studies are needed to better elucidate this mechanism.

Currently recommended dexmedetomidine dosing for maintenance therapy is $0.2\text{--}0.7 \mu\text{g}/\text{kg}/\text{hr}$ with prior evidence suggesting that there is no associated improvement in sedation quality with a dose above $1.5 \mu\text{g}/\text{kg}/\text{hr}$ (28, 29). The findings in this study suggest that high doses of dexmedetomidine infusion are associated with hyperpyrexia in a dose-dependent fashion in critically ill patients with COVID-19. Based on prior evidence and observations made in this case series, it seems reasonable to limit dexmedetomidine

dosing to less than 1.5 µg/kg/hr in patients who are later in their COVID-19 disease course whenever clinically possible.

The results also suggest that the time to fever development after initiation on dexmedetomidine is variable. It is notable that for the three patients, the average reported day of illness at the time of hyperpyrexia was day 14 (average 14.67 ± 1.53 d), which may coincide with a hyperinflammatory state, as increases in serum IL-6, IL-1 β , and tumor necrosis factor have been documented during the later phases of the COVID-19 illness (30, 31).

In prior retrospective reviews, patients with obesity were suggested to have higher risks of dexmedetomidine-associated hyperthermia (15) and obesity has also been suggested as a risk factor for COVID-19 related mortality (32). This may be related to a state of chronic low-grade inflammation that has been well established in patients with obesity (33). Indeed, two of our three patients had obesity, possibly predisposing them further to dexmedetomidine-related reactions.

As with any case series, conclusions drawn from this report are limited by sample number, selection bias, and the lack of a comparison group. This brief report calls for more rigorous clinical trials involving the use of dexmedetomidine in patients admitted to the ICU for COVID-19. Frontline providers should be aware of the association between high-dose dexmedetomidine and hyperpyrexia, particularly in critically ill COVID-19 patients who may be at increased risk of complications due to a hyperinflammatory state.

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Drs. Czepiel and Lucas contributed equally and should be considered co-first authors.

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REFERENCES

- Wu F, Zhao S, Yu B, et al: Author correction: A new coronavirus associated with human respiratory disease in China. *Nature* 2020; 580:E7
- Phua J, Weng L, Ling L, et al: Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. *Lancet Respir Med* 2020; 8:506–551
- Cheung JC, Ho LT, Cheng JV, et al: Staff safety during emergency airway management for COVID-19 in Hong Kong. *Lancet Respir Med* 2020; 8:e19
- Shehabi Y, Howe BD, Bellomo R, et al; ANZICS Clinical Trials Group and the SPICE III Investigators: Early sedation with dexmedetomidine in critically ill patients. *N Engl J Med* 2019; 380:2506–2517
- Pasin L, Landoni G, Nardelli P, et al: Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: A meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2014; 28:1459–1466
- Paris A, Tonner PH: Dexmedetomidine in anaesthesia. *Curr Opin Anaesthesiol* 2005; 18:412–418
- Iirola T, Aantaa R, Laitio R, et al: Pharmacokinetics of prolonged infusion of high-dose dexmedetomidine in critically ill patients. *Crit Care* 2011; 15:R257
- Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators: Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: Two randomized controlled trials. *JAMA* 2012; 307:1151–1160
- Pasin L, Greco T, Feltracco P, et al: Dexmedetomidine as a sedative agent in critically ill patients: A meta-analysis of randomized controlled trials. *PLoS One* 2013; 8:e82913
- Turunen H, Jakob SM, Ruokonen E, et al: Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: An economic evaluation. *Crit Care* 2015; 19:e7
- Faust AC, Sutton SE: Dexmedetomidine-associated fever in the intensive care unit. *Ther Adv Drug Saf* 2015; 6:234–237
- Grayson K, Tobin AE, Lim TK, et al: Dexmedetomidine-associated hyperthermia: A retrospective cohort study of intensive care unit admissions between 2009 and 2016. *Anaesth Intensive Care* 2017; 45:727–736
- Krüger BD, Kurmann J, Corti N, et al: Dexmedetomidine-associated hyperthermia: A series of 9 cases and a review of the literature. *Anesth Analg* 2017; 125:1898–1906
- Straw LB, Dodson CR, Schrifft DS: Dexmedetomidine-induced fever and delirium: A case report. *J Clin Pharm Ther* 2018; 43:430–433
- Thompson RZ, McDonald L, Ziemba K, et al: Dexmedetomidine-associated fever in a critically ill obese child. *J Pediatr Pharmacol Ther* 2018; 23:486–489
- Del Bene VE: Temperature. In: *Clinical Methods: The History, Physical, and Laboratory Examinations*. Third Edition. Walker HK, Hall WD, Hurst JW (Eds) Boston, Butterworth Publishers, 1990, pp 990–993
- Hussein O, Torbey M: Hyperpyrexia as the presenting symptom of intracranial hypotension. *Neurocrit Care* 2018; 28:395–399
- Walter EJ, Hanna-Jumma S, Carraretto M, et al: The pathophysiological basis and consequences of fever. *Crit Care* 2016; 20:200
- Vincent JL, Taccone FS: Understanding pathways to death in patients with COVID-19. *Lancet Respir Med* 2020; 8:430–432
- Suwanwongse K, Shabarek N: Hyperpyrexia in patients with COVID-19. *J Med Virol* 2020 Jun 10. [online ahead of print]
- Naranjo CA, Busto U, Sellers EM, et al: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239–245
- The Uppsala Monitoring Centre: The Use of the WHO-UMC System for Standardised Case Causality Assessment. 2018. Available at: <http://www.who-umc.org/graphics/4409.pdf>. Accessed April 25, 2020
- Bhatraju PK, Ghassemieh BJ, Nichols M, et al: Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020; 382:2012–2022
- Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19: Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382:1708–1720
- Huang C, Wang Y, Li X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497–506
- Pascarella G, Strumia A, Piliiego C, et al: COVID-19 diagnosis and management: A comprehensive review. *J Intern Med* 2020; 288:192–206
- Lähdesmäki J, Sallinen J, MacDonald E, et al: Alpha2-adrenergic drug effects on brain monoamines, locomotion, and body temperature are largely abolished in mice lacking the alpha2A-adrenoceptor subtype. *Neuropharmacology* 2003; 44:882–892
- Naaz S, Ozair E: Dexmedetomidine in current anaesthesia practice- a review. *J Clin Diagn Res* 2014; 8:GE01–GE04
- VenCn M, Newman J, Grounds M: A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. *Intensive Care Med* 2003; 29:201–207
- Sanders JM, Monogue ML, Jodlowski TZ, et al: Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. *JAMA* 2020; 323:1824–1836
- Shi Y, Wang Y, Shao C, et al: COVID-19 infection: The perspectives on immune responses. *Cell Death Differ* 2020; 27:1451–1454
- Kassir R: Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; 21:e13034
- Lee H, Lee IS, Choue R: Obesity, inflammation and diet. *Pediatr Gastroenterol Hepatol Nutr* 2013; 16:143–152