February 2019 Featured Articles, Volume 228

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Article 1: Burn, Trauma, Critical Care; General Surgery
Young and aged blunt trauma patients display major differences in circulating inflammatory mediator profiles after severe injury. Lamparello AJ, Ramas RA, Abdul-Malak O, et al. J Am Coll Surg 2019;228:148–160

Article 2: Liver, Biliary, Pancreas; General Surgery
Outcomes after pancreatectomy with routine pasireotide usage. Kunstman JW, Goldman DA, Gönen M, et al. J Am Coll Surg 2019;228:161–170

Objectives: After reading the featured articles published in this issue of the *Journal of the American College of Surgeons* (JACS), participants in this journal-based CME activity should be able to demonstrate increased understanding of the material specific to the article featured and be able to apply relevant information to clinical practice.

A score of 75% is required to receive CME and Self-Assessment credit. The JACS Editor-in-Chief does not assign a manuscript for review to any person who discloses a conflict of interest with the content of the manuscript. Two articles are available each month in the print version, and usually **4 are available online for each monthly issue, going back 24 months.**

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ARTICLE 1

(Please consider how the content of this article may be applied to your practice.)

Young and aged blunt trauma patients display major differences in circulating inflammatory mediator profiles after severe injury

Lamparello AJ, Ramas RA, Abdul-Malak O, et al
J Am Coll Surg 2019;228:148–160

Learning Objectives: After study of this article, surgeons should be able to understand how the differential immune response after severe traumatic injury in aged patients may contribute to clinical outcomes. This should also be taken into consideration when testing the use of immune therapies in trauma populations.

Question 1

Which of the following is TRUE regarding the immune response after trauma?

a) Trauma causes an excessive proinflammatory response followed by a compensatory anti-inflammatory response.
b) Dysregulation of the immune response after injury does not contribute to complicated clinical courses.
c) Trauma causes a simultaneous induction of innate immunity and suppression of adaptive immunity with release of both pro- and anti-inflammatory mediators.
d) Patients who have sustained the same injury will demonstrate similar immune response profiles regardless of sex or age.

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e) Injury severity does not influence immune response profiles or inflammation biomarker levels.

Critique: The paradigm regarding the immune response after trauma has changed in recent years. It was previously believed that a "systemic inflammatory response syndrome (SIRS)" state occurred immediately after traumatic injury, followed sequentially by a "compensatory anti-inflammatory response (CARS)" state. New evidence has shown, however, that immediately after trauma there is a so-called "genomic storm," with simultaneous release of immune and inflammatory mediators that have a variety of roles. In severe blunt trauma, the early leukocyte genomic response is consistent with simultaneously increased expression of genes involved in the systemic inflammatory, innate immune, and compensatory anti-inflammatory responses, as well as in the suppression of genes involved in adaptive immunity. In addition, multiple patient-specific and trauma-induced factors influence the levels of circulating inflammation biomarkers.

Question 2

As compared with young trauma patients with the same degree of injury severity, aged patients are likely to have:

a) Sustained a greater degree of injury to the extremities
b) Fewer requirements for blood transfusion
c) Greater likelihood of discharge home
d) Fewer major comorbidities
e) Increased rate of complication including nosocomial infection and longer hospital length of stay

Critique: Clinical outcomes of aged trauma patients differ significantly from those of the young. At a given level of injury severity, aged patients are more likely to develop complications. Furthermore, aged patients may sustain a similar degree of injury severity as young patients with mechanisms that involve lower energy (more falls in the aged vs more motor vehicle crashes in the young). Studies have shown that aging correlates with differential outcomes including, but not limited to, organ failure, longer ICU and hospital lengths of stay, increased likelihood of discharge to nursing or rehabilitation facility, and increased mortality.

Question 3

A 78-year-old man presents to the emergency department after a fall from standing. He is found to have multiple rib fractures and a pulmonary contusion. As compared with a younger patient with the same degree of injury severity, the plasma concentration of interleukin-6 (IL-6) in this patient after trauma is expected to be:

a) Significantly increased acutely
b) Significantly increased late
c) Not different acutely or late
d) Significantly decreased acutely
e) Significantly decreased late

Critique: Age-associated changes of the immune system are referred to as immunesenescence, which is generally viewed as a decline of adaptive and innate immune responses. This may explain why certain components of the immune response, such as IL-6 production, are severely impaired in aged patients after trauma. In young patients, however, IL-6 has been shown to have a robust and early peak within the first 24 hours after injury. IL-6 is a proinflammatory cytokine that has been well studied in trauma populations and likely contributes to organ injury after trauma.

Question 4

Circulating levels of CXC chemokines, (chemokine ligand 9/monokine induced by gamma interferon [CXCL9/MIG] and C-X-C motif chemokine 10/interferon gamma-induced protein 10 [CXCL10/IP-10]), are shown to be significantly elevated in aged trauma patients and are key mediators of their dynamic inflammatory response after injury. CXCL9/MIG and CXCL10/IP-10 are important regulators of:

a) Type 1 immune responses by attracting cells that secrete transforming growth factor (TGF)-β
b) Type 1 immune responses by attracting Th1 lymphocytes that secrete interferon gamma (IFN-γ) and contributing to the recruitment of proinflammatory cells to sites of inflammation
c) Type 2 immune responses by recruiting interleukin (IL)-4 and IL-5 to sites of inflammation
d) Type 2 immune responses by inducing mast cell and eosinophil activation
e) Type 3 immune responses by playing a role in the differentiation of Th17 cells

Critique: Aged trauma patients demonstrate an exaggerated and sustained increase of monokine induced by gamma interferon (MIG) and IP-10 on admission and over time. These chemokines have been shown to increase with normal healthy aging, but these baseline levels are well below the exacerbated levels seen in aged trauma patients. The MIG and IP-10 bind to a common receptor, CXCR3, and act as chemoattractants for Th1 lymphocytes that secrete IFN-γ. Therefore, MIG and IP-10 are important regulators of type 1 immune responses

by contributing to the recruitment of proinflammatory cells to sites of inflammation.

ARTICLE 2

(Please consider how the content of this article may be applied to your practice.)

Outcomes after pancreatectomy with routine pasireotide usage

Kunstman JW, Goldman DA, Gönen M, et al
J Am Coll Surg 2019;228:161−170

Learning Objectives: The reader should understand the scope of complications related to postoperative pancreatic leak; know the available evidence regarding the effectiveness of somatostatin analogs in preventing pancreatic leak and why pasireotide is different; and learn the available evidence regarding pasireotide's effectiveness and the quality of that evidence.

Question 1

How many of the 5 endogenous somatostatin receptors are bound by octreotide and how many are bound by pasireotide?

a) 1 by octreotide and 1 by pasireotide
b) 2 by octreotide and 4 by pasireotide
c) 1 by octreotide and 4 by pasireotide
d) 4 by octreotide and 1 by pasireotide
e) 2 by octreotide and 1 by pasireotide

Critique: Five endogenous somatostatin receptors exist. Octreotide has demonstrable activity at only 1 of these receptors (sst2), which has been 1 rationale for the limited effectiveness of octreotide in mitigating clinically relevant postoperative pancreatic fistulas. Pasireotide has activity at 4 of the 5 endogenous receptors.

Question 2

Pasireotide was originally shown to reduce the risk of pancreatic leak-related complications in what manner of study?

a) Case series
b) Retrospective case-control
c) Single-arm clinical trial
d) Single-institution randomized trial compared with placebo
e) Multi-institution randomized trial compared with placebo

Critique: Multiple methodologies for decreasing the incidence of postoperative pancreatic leak have been described, ranging from occluding the pancreatic duct, local therapies such as fibrin glue, different techniques of pancreatic anastomotic construction, and many others. Pasireotide is unique in that the initial study examining its efficacy in pancreatic surgery was of high quality in being a randomized double-blinded trial controlled by placebo. However, it was performed only at a single institution. The trial's applicability to other centers has been questioned.

Question 3

Somatostatin analogues result in all the following physiologic effects EXCEPT:

a) Decreased volume of pancreatic secretions
b) Decreased potency (ie lower concentration of amylase) of pancreatic secretions
c) Increase biliary flux by increasing cholecystokinin secretion
d) Decreased portal venous pressure
e) Decrease growth hormone secretion from the pituitary gland

Critique: Somatostatin analogues effectively mimic the effects of endogenous somatostatin, decreasing the volume and potency of most gastrointestinal secretions, including bile. It also decreases portal venous pressure, which is the rationale for administering octreotide in cases of active variceal bleeding. Similarly, inhibition of growth hormone activity is the rationale for administering somatostatin analogues (like pasireotide) for acromegaly.

Question 4

Which of the following is the most common toxicity associated with post-pancreatectomy pasireotide administration?

a) Nausea
b) Prolonged QT interval
c) Pruritis
d) Myelosuppression
e) Hemorrhage

Critique: Nausea is by far the most common symptomatic toxicity after pasireotide administration, occurring in up to half of patients. It usually occurs immediately after injection and can be mitigated by typical antiemetic agents such as ondansetron (which may be given prophylactically). It is rarely dose-limiting, however. Hyperglycemia is also frequent but again, rarely dose-limiting. None of the other toxicities mentioned occur more frequently in the pasireotide compared with the placebo group.

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ANSWERS

Article 1	Article 2
Question 1 _____	Question 1 _____
Question 2 _____	Question 2 _____
Question 3 _____	Question 3 _____
Question 4 _____	Question 4 _____

Evaluation Form

Article 1	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1. Topics and content were consistent with learning objectives.	O	O	O	O	O
2. Content was relevant to my educational needs.	O	O	O	O	O
3. I will seek additional information on this subject.	O	O	O	O	O
4. The article and questions were relevant to my practice.	O	O	O	O	O
5. Content was fair, objective, and unbiased.	O	O	O	O	O
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Article 2					
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2. Content was relevant to my educational needs.	O	O	O	O	O
3. I will seek additional information on this subject.	O	O	O	O	O
4. The article and questions were relevant to my practice.	O	O	O	O	O
5. Content was fair, objective, and unbiased.	O	O	O	O	O
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