Increased Complications with Preoperative Hyponatremia

Surgical patients with hyponatremia have an elevated risk of death and complications in the 30 days postoperatively, according to a report in the Archives of Internal Medicine.

A national quality improvement database was used to identify more than 940,000 patients undergoing major surgery at U.S. hospitals from 2005 through 2010. Based on a sodium level less than 135 mEq/L, 7.8 percent of patients had preoperative hyponatremia. Adverse outcomes in the 30-day perioperative period—including death, major coronary events, wound infections, and pneumonia—were compared for patients with hyponatremia versus normal serum sodium levels.

Thirty-day mortality was 5.2 percent for patients with hyponatremia versus 1.3 percent for those with normal baseline sodium: adjusted odds ratio (OR) 1.44. Hyponatremia was associated with increased mortality across a wide range of patient subgroups. The increase in mortality was more pronounced for hyponatremic patients undergoing nonemergency surgery, OR 1.59; and those in American Society of Anesthesiologists class 1 and 2, OR 1.93.

Several morbidity outcomes were also increased among patients with preoperative hyponatremia, including major coronary events, OR 1.21; pneumonia, OR 1.24; and wound infections, OR 1.17. For most procedures, patients with hyponatremia had approximately a one-day increase in median length of stay.

Hyponatremia is a known, potentially reversible risk factor for adverse outcomes in medically ill inpatients. This large database study links preoperative hyponatremia to an increased risk of perioperative morbidity and mortality after major surgery. Discussing the clinical implications, the researchers write, “One reasonable approach is to monitor for perioperative complications in all patients at risk and to selectively treat hyponatremia before nonemergency surgical procedures when a reversible cause is found” [Leung AA, et al: Preoperative hyponatremia and perioperative complications. Arch Intern Med. 2012; 172: 1-8].

Low Blood Pressure Doesn’t Reduce Mortality in Type 2 Diabetes

Aggressive blood pressure reduction in the year after diagnosis of type 2 diabetes does not lead to a reduced risk of death, according to a study of primary care data in the British Medical Journal.

The researchers analyzed data from nearly 127,000 adult patients with type 2 diabetes newly diagnosed at U.K. general practices between 1990 and 2005. Systolic and diastolic blood pressures during the subsequent year were analyzed for association with mortality. Comparisons were made for patients with and without established cardiovascular disease—present in 9.8 percent of patients at baseline. Median follow-up was 3.5 years.

With adjustment for a wide range of baseline characteristics, “tight” control of blood pressure to less than 130/80 mm Hg was not associated with increased survival in patients with cardiovascular disease. For patients with systolic blood pressure of 110 mm Hg, the hazard ratio

For renal transplant patients...

**myfortic®**: Consistent From Refill to Refill

Potential MMF REFILL CALENDAR

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**myfortic** REFILL CALENDAR

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- Multiple companies offer a generic version of CellCept® (mycophenolate mofetil)
  - Presently, there are 11 manufacturers of generic CellCept®
  - 11 different MMF tablets (500 mg) and 10 different MMF capsules (250 mg) are available
- **myfortic** is the only patented-protected MPA
  - Produced only by Novartis
  - 1 manufacturer in 1 facility

When you prescribe myfortic, your patients get myfortic... consistent from refill to refill

More than 81% of myfortic prescriptions had a $0 co-pay with the Novartis Monthly Co-pay Card for eligible patients.

Help support your patients throughout their transplant experience by having them visit www.myfortic.com/jr2 where they can sign up to receive relevant educational information.

**myfortic** and CellCept or MMF should not be used interchangeably without physician supervision because the rate of absorption following the administration of these products is not equivalent.

- **MMF**, mycophenolate mofetil; **MPA**, mycophenolic acid.
- **CELLCEPT** is a registered trademark of Hoffmann-La Roche Inc.
- †Product coverage and program subject to change without notice.
- ‡Based on data from the myfortic Co-pay Savings Program. Initial prescription or refills based on 1-year (2011) transaction data for cash payment and insured patients combined.

**Indication**: **myfortic** (mycophenolic acid) delayed-release tablet is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

**Important Safety Information**:

**WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES, AND SERIOUS INFECTIONS**

- Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations.
- Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.
- Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe **myfortic** (mycophenolic acid) delayed-release tablet. Patients receiving **myfortic** should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

- **myfortic** is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid (MPA), mycophenolate mofetil (MMF), or to any of its excipients.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent pages.
for death was 2.79, compared to those with ‘usual control’—systolic blood pressure 130 to 139 mm Hg. For diastolic blood pressure, hazard ratios for death were 1.32 at 70 to 74 mm Hg and 1.89 at less than 70 mm Hg, compared to usual control of 80 to 84 mm Hg.

Lower blood pressure targets were also associated with increased mortality among patients without cardiovascular disease. Similar patterns were found on analysis of patients receiving treatment for diagnosed hypertension.

Aggressive blood pressure reduction has been recommended for high-risk patients with diabetes, cardiovascular disease, or kidney disease. The new data suggest that lowering blood pressure to less than 130/80 mm Hg may be associated with increased, rather than decreased, all-cause mortality. The risk may be greatest at blood pressures less than 110/75 mm Hg [Vamos EP, et al: Association of systolic and diastolic blood pressure and all-cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study. BMJ 2012; 345: e5567].

**Important Safety Information: (cont)**

**Embryofetal Toxicity: myfortic® can cause fetal harm when administered to a pregnant female. Use of myfortic® during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital anomalies.**

**Pregnancy Exposure Prevention and Planning:** FRP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning information below.)

**Lymphoma and Other Malignancies:** Patients receiving immunosuppressive regimens involving combinations of drugs, including myfortic® as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

**Infections:** Overexpression of the immune system can also increase susceptibility to infection, fatal infections, and sepsis.

**Polyomavirus Infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving myfortic®, PVAN, especially due to BK virus infection, is associated with severe outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN.

**Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia.** Risk factors for PML include treatment with immunosuppressive therapies and impairment of immune function.

In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft.

**Blood Dyscrasias Including Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving myfortic® should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.3 x 10^9/L] or anemia), dosing with myfortic® should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

**Pregnancy Testing:** To prevent unplanned exposure during pregnancy, FRP should be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning information below.)

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**Contraception:** FRP taking myfortic® must receive contraceptive counseling and use acceptable contraception during the entire myfortic® therapy, and for 6 weeks after stopping myfortic®, unless the patient chooses abstinence. Patients should be aware that myfortic® reduces blood levels of the hormones in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females)

**Pregnancy Planning:** For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of myfortic® should be discussed with the patient.

**Gastrointestinal Disorders:** Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) and maintenance patients (1.3%) treated with myfortic® (up to 12 months).

**Patients with Renal Impairment:** Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

**Concurrent Medications:** Caution should be used with drugs that interfere with enterohepatic recirculation because of the potential to reduce efficacy.

**Hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) Deficiency:** myfortic® should be avoided in patients with HGPRT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

**Immunizations:** Use of live attenuated vaccines should be avoided.

**The principal adverse reactions associated with the administration of myfortic® include constipation, nausea, and urinary tract infection in de novo patients and nausea, diarrhea, and nasopharyngitis in maintenance patients.

**References:**


Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent pages.