

Human Factors Affecting Infection Prevention

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cilitators of infection prevention, along with workflow scheduling and variation in policies and procedures. Staff at several facilities cited factors associated with a supportive culture, including the presence and engagement of facility leadership during work hours. Staff also identified extrinsic patient factors leading to disruptions in the flow of care, including hygiene, transportation, vascular assess, and hemostasis.

This small, exploratory study identifies

macroergonomic factors potentially affecting infection prevention practices during dialysis care. “[T]he complex constellation of human skills required for the optimal completion of infection prevention tasks within dialysis may be significantly affected (both positively and negatively) by the design of our systems of care,” the researchers write. Further studies are needed to incorporate the observations into strategies to reduce infection risks [Parker SH, et al. Human factors contributing to infection prevention in outpatient hemodialysis centers: A mixed methods study. *Am J Kidney Dis*, published online March 4, 2024. doi: 10.1053/j.ajkd.2023.12.024]. ■

Cefepime-Taniborbactam Is Superior to Meropenem for Complicated UTI

The β -lactam and β -lactamase inhibitor combination cefepime-taniborbactam offers a higher treatment success rate in the treatment of complicated urinary tract infection (UTI) compared with meropenem, reports a clinical trial in *The New England Journal of Medicine*.

The phase 3 “Safety and Efficacy Study of Cefepime/VNRX-5133 in Patients with Complicated Urinary Tract Infections” (CERTAIN-1) trial enrolled 661 patients

with complicated UTI. Patients were randomly assigned in a 2:1 ratio to treatment with cefepime-taniborbactam (2.5 g intravenously [IV]) or meropenem (1 g IV), every 8 hours for 7 days. In patients with bacteremia, treatment could be extended to 14 days.

Microbiologic and clinical success rates were assessed at 19 to 23 days in a microbiologic intention-to-treat population of 436 patients with positive urine culture for a qualifying gram-negative pathogen, most

TARPEYO® (budesonide) delayed release capsules

Brief Summary of Prescribing Information

4 CONTRAINDICATIONS

TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy [see *Dosing and Administration (2)*] or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) [see *Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

5.2 Risks of Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3 Other Corticosteroid Effects

TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypercorticism and adrenal suppression [see *Warnings and Precautions (5.1)*]
- Risks of immunosuppression [see *Warnings and Precautions (5.2)*]
- Other corticosteroid effects [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TARPEYO was evaluated in 389 patients in the randomized, double-blind, placebo-controlled study, NeflgArd (NCT: 03643965, Phase 3 clinical study in adults with primary IgAN). The data below reflect TARPEYO exposure in 195 patients with a median duration of 41 weeks, compared with comparable exposure to placebo in 194 patients.

The most common adverse reactions, reported in greater than or equal to 5% of TARPEYO-treated patients and greater than or equal to 2% higher than placebo, in the 9-month treatment period are listed in *Table 1*.

Most adverse reactions that occurred at a greater incidence for TARPEYO compared to placebo were consistent with hypercortisolism and reversible, resolving within 3 months after discontinuation.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of TARPEYO treated patients, and greater than or equal to 2% higher than Placebo

Adverse Reaction	TARPEYO 16 mg (N=195)	Placebo (N=194)
	n (%)	n (%)
Peripheral edema	33 (17)	10 (5)
Hypertension	23 (12)	6 (3)
Muscle spasms	23 (12)	8 (4)
Acne	22 (11)	2 (1)
Headache	19 (10)	14 (7)
Upper respiratory tract infection	16 (8)	12 (6)
Face edema	15 (8)	1 (0.5)
Weight increased	13 (7)	6 (3)
Dyspepsia	13 (7)	4 (2)
Dermatitis	12 (6)	2 (1)
Arthralgia	12 (6)	4 (2)
White blood cell count increased	11 (6)	1 (0.5)

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine [see *Clinical Pharmacology (12.3)*].

Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism (see *Clinical Considerations*). In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels (see *Data*).

commonly Enterobacterales species. In this group, the mean age was approximately 56 years, and 53% of patients were women. The diagnosis was complicated UTI in 57.8% of patients and acute pyelonephritis in 42.2%.

Composite microbiologic and clinical success rates were 70.6% with cefepime-taniborbactam versus 58.0% with meropenem. A prespecified superiority analysis showed a significant 12.6 percentage-point difference between groups. At late follow-up (28 to 35 days), composite and clinical success rates remained higher with cefepime-taniborbactam. Among patients with bacteremia, composite success rates at test of cure were 81.6%

with cefepime-taniborbactam versus 68.4% with meropenem.

Headache, gastrointestinal events, and hypertension were the most common adverse events with cefepime-taniborbactam. Serious adverse events occurred in approximately 2% of both groups.

Emerging resistance to β -lactam antibiotics poses a challenge to treatment of complicated UTI, as for other serious infections. The cefepime-taniborbactam combination has shown promise for treatment of serious gram-negative infections.

The CERTAIN-1 findings suggest that cefepime-taniborbactam is superior to

meropenem for treatment of complicated UTI including acute pyelonephritis. Safety profiles are similar between the two treatments. Cefepime-taniborbactam is “a potential treatment option for patients with complicated UTI and acute pyelonephritis caused by Enterobacterales species and *Pseudomonas aeruginosa*, including antimicrobial-resistant strains,” the investigators conclude [Wagenlehner FM, et al.; CERTAIN-1 Study Team. Cefepime-taniborbactam in complicated urinary tract infection. *N Engl J Med* 2024; 390:611–622. doi: 10.1056/NEJMoa2304748]. ■

Racial Differences in ADPKD Mortality for Older Adults

A large analysis of patients with autosomal-dominant polycystic kidney disease (ADPKD) finds differences in mortality risk for Black versus White patients aged 65 years or older, reports a study in *BMC Nephrology*.

The researchers analyzed US Renal Data System data for patients with ADPKD from 2014 through 2016. The analysis included a cohort of 1936 patients with non-end stage renal disease (ESRD) chronic kidney disease (CKD) and a cohort of 37,461 patients with ESRD. The mean age was 71.4 years in the cohort with non-ESRD CKD and age 59.2 years in the cohort with ESRD. Race was classified as White in 79.6% and 73.8%, respectively.

After adjustment for age, mortality was 18.4 per 1000 patient-years in patients with ADPKD with non-ESRD CKD and 37.4 per 1000 patient-years for those with ADPKD and ESRD. On Cox regression modeling in the cohort with non-ESRD CKD, risk of death was higher for patients with more advanced disease: hazard ratio (HR), 1.59 for stage 4 and 2.71 for stage 5 CKD compared with stage 3. In the cohort with ESRD, risk of death was more than twice as high among patients undergoing dialysis: HR, 2.36.

Among patients with non-ESRD CKD aged 65 years or older, age-adjusted mortality was highest for Black patients: 82.7 deaths per 1000 patient-years. In contrast, among older adults in the cohort with ESRD, mortality was highest for White patients: 136.1 deaths per 1000 patient-years.

The study revealed findings regarding mortality specific to patients with ADPKD, the leading inherited cause of ESRD. For patients aged 65 or older with ADPKD and ESRD, the data show a “numerically lower” mortality compared with previous reports, possibly reflecting “more effective treatment and disease management.”

In the same age group, the findings suggest racial differences in both cohorts of non-ESRD CKD and ESRD of patients with ADPKD, with a possible survivorship effect among Black patients. “Black patients may be less likely than other racial groups to survive long enough to reach ESRD, perhaps because of inequities in care,” the researchers write. “ADPKD also may be underdiagnosed in Black patients with a hypertension comorbidity” [Mladi D, et al. Mortality risk in patients with autosomal dominant polycystic kidney disease. *BMC Nephrol* 2024; 25:56. doi: 10.1186/s12882-024-03484-3]. ■

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

Fetal/Neonatal Adverse Reactions Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly [see Warnings and Precautions (5.1)].

Data

Animal Data Budesonide was teratogenic and embryo-lethal in rabbits and rats.

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).

Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis).

In a peri- and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures ≥ 0.012 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary Breastfeeding is not expected to result in significant exposure of the infant to TARPEYO. Lactation studies have not been conducted with oral budesonide, including TARPEYO, and no information is available on the effects of the drug on the breastfed infant or the effects on the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide (see Data). Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TARPEYO and any potential adverse effects on the breastfed infant from TARPEYO, or from the underlying maternal condition.

Data One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.

Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg TARPEYO. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.4 Pediatric Use

The safety and efficacy of TARPEYO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TARPEYO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]. Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

10 OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of corticoids are rare.

In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

Please see Full Prescribing Information for TARPEYO at TARPEYOhcp.com

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