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The Script

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340B Drug Pricing Program

By Christopher M. Brown, Pharm.D., BCPS

Pictured: Donna Wilk, CPhT and Kara Cornell, MHA

Section 340B of the Public Health Service Act requires manufacturers to sell prescription drugs at discounted prices to covered entities that provide care to uninsured, low-income patients, and vulnerable communities. Thanks to this section, manufacturers are imposed a 'ceiling' price that they may charge for drugs sold to covered entities. This usually translates into tremendous savings for those covered entities.

To become covered, you must meet eligibility requirements, register with the 340B Program, and comply with all the 340B program requirements. The registration process must be done online during the first two weeks of any calendar quarter and don't take effect until the next quarter. Additionally, the process is tedious and time intensive, but towards the end of January 2023 a savvy team—Brad Foster, Pharm.D., Donna Wilk, CPhT, and Kara Cornell, MHA—decided to take the leap and apply to become a covered entity. It took countless hours of effort to ensure Norman Regional Health System (NRHS) met all the requirements and became a covered entity in time. There were many issues that needed addressed, but ultimately NRHS was successfully admitted into the 340B drug pricing program. While discussing this article, Brad wanted almost all the credit to go to Donna and Kara, who did most of the work. When speaking with Donna and Kara, they let me know how much work Zack Myers with HIT spent working on his end to ensure our data pulls and interfaces worked appropriately.

Thanks to all of them, we began receiving 340B drug pricing in April 2023. Their hard work paid off and saved NRHS nearly $800,000 that first quarter. (continued on page 2)

In This Issue:

Please share your thoughts, comments, and/or suggestions with us.

Do you have an idea for an article? Is there more information we can provide to you?

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NORMAN REGIONAL Health System

340B Drug Pricing Program (continued)

By Christopher M. Brown, Pharm.D., BCPS

Now that NRHS is a 340B entity, our medication procurement has become exponentially more complicated. For instance, we are only allowed to order a drug with 340B pricing when we have obtained an "accumulation." Meaning that we need to prove that a patient had a drug order for the medication we are trying to replace. Without the accumulation and ability to purchase the drug with 340B pricing, we are required to purchase at the wholesale acquisition cost (WAC). Unfortunately, WAC is more expensive than what we would have paid when we were not a 340B covered entity.

It's a complicated process, but Brad, Donna, Kara, and Zack are committed to ensuring NRHS continues to save as much money as possible. Based on our savings to date, we are estimating that **NRHS will save well over $4 million per year!**

Cefepime-Induced Neurotoxicity

By Sarah El-Koubysi, Pharm.D.

Cefepime is a commonly used antibiotic with a broad spectrum of activity. First approved for use in 1996, it is effective against pneumonia, intra-abdominal infections, and skin and soft tissue infections. Despite its utility, cefepime-induced neurotoxicity (CIN) is a worrisome adverse effect and risk is elevated in patients with renal dysfunction. The exact mechanism by which cefepime causes neurotoxicity is not well understood. However, it is thought to be related to gamma-aminobutyric acid (GABA) inhibition and subsequent hyper-excitation of neurons in the central nervous system (CNS).

The estimated incidence of CIN ranges from 0.15% of all patients, up to 15% in critical care patients. The most common symptoms are diminished level of consciousness (80%), disorientation (47%), myoclonus (40%), and non-convulsive status epilepticus (31%). See table below for more symptoms. CIN should be suspected when changes in neurological function occur within two to five days after initiation of cefepime and other causes of altered mental status have been excluded. The most common predisposing risk factors for CIN include decreased renal function, inappropriate dosing regimen, and older age. Additionally, sepsis, CNS infections, and previous brain injuries may alter the integrity of the blood brain barrier, which can result in an up to 45% increase in CNS penetration of cefepime.

Common Symptoms of Cefepime-Induced Neurotoxicity
Altered mental status
Reduced consciousness
Myoclonus
Confusion
Aphasia
Seizures
Agitation
Hallucination
Encephalopathy

CIN is reversible in most patients. The only definitive treatment is early identification and discontinuation of cefepime. Once discontinued, clinical improvement is often seen within one to three days. However, in emergent situations hemodialysis may be considered. CIN is best prevented through careful dose adjustments in patients with renal dysfunction and creating awareness of this adverse drug reaction among healthcare professionals.

At NRHS, we conducted a retrospective study to identify patients in the intensive care setting with cefepime-induced neurotoxicity. We studied a years' worth of data and were able to include 64 patients in our study. Ultimately, four (6.25%) patients were identified as having symptoms of cefepime-induced neurotoxicity. This is well below the estimate of up to 15% in the critical care setting. Potentially, the biggest reason for our reduced incidence of CIN is the pharmacy's renal dosing program, where patients with altered kidney function on cefepime are monitored daily. This gives us the opportunity to identify patients at risk and make adjustments to their dosing regimens as needed. However, our study period did take place during a time where coronavirus was rampant, and patients were much more likely to be mechanically ventilated and sedated for long periods of time. Therefore, we were likely unable to appropriately monitor those patients for symptoms of CIN. Electronic medical record documentation may have also played a role in our lower than average identification of events. **This is why it is vitally important for members of the healthcare team to help identify, monitor, and report new neurological changes in our patients and document those changes.** Doing so will help limit potential adverse drug effects and ensure our patients have the best possible outcomes.

Augmented Renal Clearance

By Trevor Sanders, Pharm.D.

Augmented renal clearance (ARC), defined as creatinine clearance ≥130 mL/min/1.73 m^2, is a growing concern in critically ill patients. Many medications are dose adjusted in patients exhibiting decreased renal function to prevent toxicity and other adverse events. However, dose adjustments are not common practice in patients with ARC, which, as we are discovering, may subject them to less-than-optimal treatment regimens.

There is a growing body of evidence that suggests patients with ARC have worse clinical outcomes. Especially in patients who are critically ill and receiving hydrophilic antibiotics, such as beta-lactam antibiotics. Risk factors for ARC include male patients who are younger in age, have poly-trauma, illnesses lower in severity, or increased cardiac output due to fluid resuscitation, vasopressor use, or critical illness (see table on right).

Risk Factors Associated with Augmented Renal Clearance	
Male Sex	Younger Age
Poly-Trauma	Lower Severity Illness
Increased Cardiac Output	Fluid Resuscitation
Vasopressor Use	Critical Illness

Beta-lactam antibiotics, such as those listed in the table below, have all been implicated for worse outcomes in patients with ARC. Beta-lactam efficacy is dependent on serum concentrations remaining above the minimum inhibitory concentration (MIC) of the bacteria for at least 50-70% of the dosing interval. This can be monitored directly through therapeutic drug monitoring techniques, however the availability of these labs are limited.

Common Antibiotics Associated with Augmented Renal Clearance
Ampicillin-sulbactam (Unasyn®)
Cefepime (Maxipime®)
Ceftaroline (Teflaro®)
Ceftazidime (Fortaz®)
Ceftriaxone (Rocephin®)
Meropenem (Merrem®)
Piperacillin-tazobactam (Zosyn®)

In the absence of therapeutic drug monitoring in most hospital systems, clinicians must consider patient factors such as time to defervescence, leukocytosis resolution, respiratory requirements, repeat positive bacterial cultures, and overall clinical picture to determine if antibiotics are working adequately to resolve the infection. In patients with ARC these factors may not improve, or unexpectedly worsen, while receiving beta-lactam antibiotic therapy.

Currently, dose adjustments are not well defined for patients experiencing ARC. Limited studies are available, however, most are based on mathematical simulations and there is extremely limited real world evidence. So far, recommendations include increasing the infusion time (e.g. extended infusion over 3 or more hours), increasing the dosing frequency, and/or increasing the dose.

The pharmacy has recently begun monitoring for patients with ARC, and when needed suggest adjustments to ensure our patients are on appropriate dosing regimens. It's important for all healthcare providers to monitor patients with augmented renal clearance to make certain they are receiving appropriate therapy.

Altered Mental Status Associated with Diphenhydramine

By Carley Welch, Pharm.D.

Diphenhydramine (Benadryl®) is a first generation antihistamine that is commonly prescribed for a variety of indications. Common indications include itching, insomnia, allergic reactions, vertigo, medication induced extrapyramidal symptoms, and many more. Diphenhydramine exhibits strong anticholinergic and sedative properties. These properties can result in a variety of undesirable adverse drug effects. Anticholinergic adverse effects include blurry vision, dry mouth, urinary retention, tachycardia, and altered mental status (AMS). (continued on page 4)

Altered Mental Status Associated with Diphenhydramine (continued)

By Carley Welch, Pharm.D.

These adverse drug events are amplified in elderly patients due to a prolonged duration of action of diphenhydramine. AMS may also lead to various other complications, especially in the elderly population. In the current literature, it is recommended to use diphenhydramine more conservatively and at reduced doses in the elderly population, but no consensus has been established.

Signs & Symptoms of Altered Mental Status

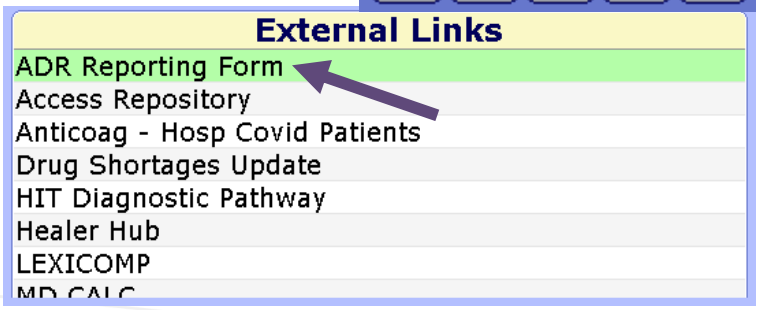
Altered Level of Responsiveness		Amnesia	Lethary
Changes in Judgement	Disorientation	Confusion	Disruption in Perception
Altered Psychomotor Skills	Labile Emotions	Disorganized Speech	

Diphenhydramine related AMS can include a variety of cognitive and behavioral symptoms, (see chart on right). The Beer's Criteria recognizes diphenhydramine, along with several other medications, as having a possible association of AMS and delirium. Sedative hypnotics, such as benzodiazepines — diazepam, midazolam, alprazolam, etc. — have also been implicated in the development of AMS and delirium. Taken together, the risk of AMS and delirium are additive. Drug related AMS increases hospitalization length of stay, long-term cognitive impairment, and even mortality.

Common Medications Associated with AMS	
Baclofen	Methocarbamol
Benzodiazepines	Orphenadrine
Carisoprodol	Oxybutynin
Cyclobenzaprine	Promethazine
Dicyclomine	Scopolamine
Eszopiclone	Tizanidine
Hydroxyzine	Zaleplon
Hyoscyamine	Zolpidem
Metaxalone	

Patients are at a higher risk of AMS when receiving diphenhydramine and concomitant central nervous system altering medications, like those listed in the table below. **Members of the healthcare team that directly interact with patients are best positioned to identify these signs and symptoms of altered mental status.**

If suspected, it is crucial to appropriately document in the medical record the associated signs and symptoms. It is also imperative to make those involved in the patient's care aware of the problem. If medications are suspected to be the cause, then this should be reported and documented as soon as possible. Luckily, NRHS has an adverse drug reaction hotline, which can be reached by simply dialing **73333** and following the directions of the recording. We also have an electronic adverse drug reaction (ADR) form located on healer hub, which may be accessed via Meditech. While on almost any screen in Meditech, click the R-globe button located in the bottom right corner (see images on the bottom right side of page). Once clicked, you will have the option of choosing a variety of links, one of which being the ADR reporting form. Click on it, then follow the instructions and when finished click submit.



Quickly identifying, notifying, reporting, and removing potential causes of AMS are the best interventions we can make on behalf of our patients to improve their lives and outcomes.

Pharmacy and Therapeutics Committee Update

Drug	Labeled Indication	Dosage and Strength	P&T Action
Urea Medical Food (Ure-na®)	Syndrome of inappropriate antidiuretic hormone (SIADH) associated hyponatremia	15 to 30 gm daily in one or two divided doses (max: 60 gm/day)	Added to formulary
Onabotuli-numtoxinA (Botox®)	Formulary use indications: neurogenic detrusor over-activity, overactive bladder, (off-label: anal fissure)	Variable: up to 600 units in divided doses	Added to formulary for use in urologic and rectal procedures
Ibuprofen lysine (NeoProfen®)	Patent ductus arteriosus closure in premature infants not more than 32 weeks gestational age (GA) when usual management is ineffective	Standard dose: initial 10 mg/kg, then 5 mg/kg at 24 hour intervals High-dose: initial 15-20 mg/kg, followed by 2 doses of 7.5-10 mg/kg at 24 hour intervals	Added to formulary for use in neonates only

Critical Medication Shortages*

By Keali O'Reilly, CPhT

MEDICATION	ACTION PLAN
Budesonide inhalation	On allocation with slightly improved availability. Interchanging orders to fluticasone HFA metered dose inhaler when able.
Bupivacaine 0.5% + epinephrine injection	Backorder with estimated time of arrival (ETA) of March 2025. Alternatives: plain bupivacaine 0.5%, lidocaine 1%, or 2%.
Butorphanol injection	Almost completely out of stock. On backorder with ETA of December 2023-February 2024. Alternatives: morphine and fentanyl injection.
Clindamycin injection	Limited allocation and backorder with no estimates for a release date.
Dobutamine 250 mg/250 mL injection	Requesting change to double strength concentration bags when possible. Current stock of 250 mg/250 mL bags are being reserved for babies. No estimates for a release date.
Ipratropium inhalation	Improving availability. Using combination of albuterol/ipratropium nebulization when able.
Ketorolac injection	Limited availability. P&T committee approved a temporary auto-stop of 24 hours on all IV ketorolac orders. Use alternative when able.
Lidocaine 2% viscous solution	Backorder with ETA of 4th quarter 2023. Stock is critically low hospital-wide.
Nalbuphine injection	Backorder with no ETA.
Olanzapine injection	Intermittently on backorder currently with improved availability. Alternatives: ziprasidone or haloperidol.
Potassium phosphate injection	Worsening availability, with ETA of October-November 2023. Please use sodium phosphate or oral phosphorus alternatives when able.
Sodium bicarbonate injection	Backorder with no ETA. Vials are currently loaded into Pyxis machines. Please conserve syringes whenever possible.

*Table is not all-inclusive. Comprehensive list of reported nationwide shortages available at https://www.ashp.org/Drug-Shortages/Current-Shortages.

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