The fact that Czechs have the highest per capita beer consumption in the whole world is starting to take on a completely different perspective in your brain. Forty-two gallons per person per year! It’s not about alcoholism. It’s not about beer being cheaper than bottled water in this crazy little country. It’s about the fact that there is something innately patriotic about beer drinking in the Czech Republic. Nicknamed “liquid bread”, beer remains the primary accompaniment to most Czech foods, conversations, and social events. There is even a beer spa (Chodovar) where you can take a bath in this liquid bread!

As you walk through the Pilsner Urquell Brewery Museum, you can sense the pride with which the citizens of Plzeň have reconstructed their history and livelihood in this authentic medieval brewing house. You feel a sense of trepidation as you walk through the birthplace of Pilsner the beer and Pilsner the name. You learn that the first mention of beer making in Plzeň was in 1307 and the brewery was founded by Plzeň citizens in 1839. In the gothic malt house, you stare into the 18 meter-deep well widely known for its remarkably soft water quality. For centuries, this well was the primary source of water for soaking the malt and allowing grains to germinate.

You then walk through the old drying shed, the 19th century laboratory, and finally the cooling cellars. These cooling cellars were among the first of their kind, allowing bottom-fermenting yeast to grow. The use of bottom-fermenting yeast was a new Bavarian technique that evolved in Germany around the 1840s: it improved the beer’s clarity and shelf life, which, prior to that, was apparently rather questionable. The first Pilsner beer, made in 1842, was the world’s first golden beer. It was a success, and the beer was quickly exported all over the Austrian Empire. There was a special train between Plzeň and Vienna that exported the beer every morning. Today, the brewery—called Plzeňský Prazdroj—produces Pilsner Urquell, Gambrinus, and Primus. The
“Eighth Prague Adventure...” Continued

Pilsner beer style, as a type of pale hoppy lager beer, is now produced by many other breweries around the world as an imitation of the original Pilsner.

At the end of the tour, you get to sample the modern Pilsner Urquell, but you also get a taste of the unfiltered non-pasteurized Pilsner brewed the old-fashioned way: fermented in open wooden kegs and matured in oak barrels in the authentic cool cellars. You diligently pull out your Czech beer catalog and proceed to list and grade both beers. Since your arrival to Prague, you've been listing all the beers you have tasted, rating them on a scale of 0 to 10. You were hoping you could identify your favorite beer, but at this point, you’re having a hard time deciding. You have read that, in the past, Velkopopovický Kozel's Medium beer has won the prize for the best Czech beer. You laugh at the thought that Czechs had to select the least pronounceable beer as their best … although you would have loved to go to Velké Popovice as well to visit the Kozel Brewery, with its real kozel mascot (a buck).

The beer consumed in largest quantity in the Czech Republic is Gambrinus, even though it’s not thought of as the best. Many Czechs are, of course, partial to Pilsner Urquell. But there are many other beers that have caught your attention: Staropramen (made by Prague's largest brewery), Bernard, Budvar, Radegast … and then there are some one-of-a-kind beers made by many small microbreweries that have appeared in the last decade (Dalešice, Pegas, richard, and many others).

Later in the afternoon, you make a point of walking through the quaint old town of the city of Plzeň. As the weather gets worse and some raindrops land on your coat, you duck into one of the pubs on the large city square. Since you won’t have time to visit the home of another major Czech beer, české Budějovice, you order a glass of Budvar, a light tasting wheat beer, typical of Czech lagers. You remember reading about the trademark dispute over Budweiser where, in 1876, a US brewer also called his beer Budweiser. This was followed by a complicated lawsuit resulting in the original Czech Budweiser to be marketed as Budějovický Budvar in the Czech Republic and Australia, Budweiser Budvar in the rest of Europe, and as Czechvar in North America. And there you go, adding Budějovický Budvar to your Czech beer catalog with an 8/10 grade.

You study your beer coaster, as you discretely scheme how to get it into your pocket without looking suspicious and ridiculous. Yes, you’ve been a classic tourist in this arena as well: pocketing beer coasters! You’re just slightly ashamed of yourself and you pretend to read with great intent the word “Budvar” and “12%” on the coaster. A few days ago you had a near heart attack when you saw the percentage and thought it referred to the percentage of alcohol in the beer you just drank. But now you know that the number instead represents the amount of malt extract used in the brewing process. A higher percentage usually comes with a stronger flavor and the percentage of alcohol is approximately a third of that number.

As you look around the pub, you remember a statement you saw on the internet before coming to Prague: “Vienna may have its Café Society, New York has its High Society, but Prague is the proud home of Pub Society.” The beer is central to the Czech pub. There is usually no loud music, although you have often seen TVs for sport watching. There are usually large wooden tables and you can rarely sit all by yourself during busy hours. There have been many times when a new beer appeared in front of you before you actually asked for one. You have also been practicing the pub terminology you learned from your Czech friend. He taught you to say “pivo” (beer) years ago, but before letting you go to Prague, he made a point of writing out for you the different words for “pub”. There is “ pivnice,” which one would
“Eighth Prague Adventure...” Continued

ISHLT Links

translate most literally as beer-house. Then there is the most common term of “hospoda,” probably the closest equivalent of pub and it serves food as a restaurant. “Hostinec” is yet another term … your Czech friend really could not find an English equivalent and said “forget it, you just need to know that they serve beer and food in there, too.” And, beer gets stored in plastic sacs that are placed in large tanks (the so-called bag-in-box method) and the beer is pressed out of the tanks using a high-pressure air compressor to avoid exposure to air, backwash, and contamination. Many pubs and restaurants have acquired these Tankovnas since the mid-1990s.

From the bus on your way back to Prague, you watch the large fields of hops and barley extending beyond the city limits. As you dream about beer, you review your beer plans for the next few days. You are hoping to make it to U Zlatého tygra where Czech President Václav Havel took Bill Clinton for a drink. The story goes that Clinton drank 3 beers and then had to cancel his daily jog the following morning.

You are also hoping to make it to U Fleků, the oldest microbrewery in Prague in existence--since 1499--and with the longest history of continuous brewing (over 500 years). The older Prague breweries are all gone, including the Benedictine Břevnov Monastery brewery that began beer brewing as early as 993 A.D. You find it quite fitting that the first breweries were based in monasteries: a testament to the fact that pivo is not a Czech habit … it’s a religion.

Disclosure Statement:
The author has no conflicts of interest to disclose.

of course, you can buy beer in pretty much any other establishment that feeds people, such as “restaurace” (restaurant) or “jídelna” (cafeteria). Beer drinking takes place any time of day from lunchtime until about 11PM. For drinking or partying later at night there are bars and “diskotéka” (disco bars).

And then there is the pervasive “U” featured in the names of the majority of pubs. For a while, you thought it was some sort of decoration … or that it perhaps meant “pub”? No, it just means “at”. “U vola” means “at the ox’s place.” Sort of like “at McDonald’s” would read “U McDonalda.”

One more piece of trivia that you have discovered is the term “Tankovna” or “beer tank” made for dispensing unpasteurized beer. All Czech beer for export is pasteurized and sterilized by heating, giving it a longer shelf life. However, the pasteurizing process can occasionally result in oxidization, leading to an unpleasant taste and odor. To avoid this terrible risk, Czechs have devised a way of drinking unpasteurized beer while decreasing the risk of bacterial contamination. The unpasteurized beer gets stored in plastic sacs that are placed in large tanks (the so-called bag-in-box method) and the beer is pressed out of the tanks using a high-pressure air compressor to avoid exposure to air, backwash, and contamination. Many pubs and restaurants have acquired these Tankovnas since the mid-1990s.

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Quotable Quotes

From Louis Pasteur:

“Where observation is concerned, chance favors only the prepared mind.”

“To bring one’s self to believe in a truth that has just dawned upon one is the first step towards progress; to persuade others is the second.” – from his Physiological Theory of Fermentation, 1879

From Alexander Fleming:

“I have been trying to point out that, in our lives, chance may have an astonishing influence and, if I may offer advice to the young laboratory worker, it would be this—never to neglect an extraordinary appearance or happening.”

“A good gulp of hot whiskey at bedtime—it's not very scientific but it helps.”

From Benjamin Franklin:

“Well done is better than well said.”

“Many complain of their memory, few of their judgment.”

From Mark Twain:

“Be careful about reading health books. You may die of a misprint.”

“Education consists mainly of what we have unlearned.”

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This is not an article about the innovative neighborhood pub, where you can drink beer and take shots until the light of day at a self-serve beer table in the lower Haight of San Francisco, named *The Mad Dog in the Fog* where soccer is called football and you can watch the World Cup. By the end of this article, you will recognize that this title has everything to do with the theme of this issue and can be summed up by our father of germ theory. He has also been considered the father of microbiology and immunology. Not unlike Lincoln, he had a poor and humble beginning and developed “inescapable forward moving logic.” But, unlike Lincoln, he received extensive formal education with an early meteoric rise from his work on crystals as a young chemist.

Because of controversies brewing in France—not with Darwin’s *Origin of Species*, but with the origin of life itself—he burst into the scene of French Science when he discovered that some crystals were identical in chemical properties and every other aspect except that they were mirror images of each other. These non-superimposable mirror images bent polarized light in opposite directions at the same angle. He boldly declared that such optical activity was associated with life and that optical inactivity was associated with death and decay. At the same time, he developed a clear understanding of fermentation. Many of the products of fermentation were optically active; therefore, he reasoned that fermentation was a consequence of the biological activity of brewer’s yeast. This knowledge of light and fermentation led him to debunk the prevailing concept of spontaneous generation which had not only greatly influenced science but also had significant social, political, and religious implications in Europe.

He was never one to pass up an opportunity to bring attention to himself in a dramatic fashion. He made impressive demonstrations of his new discoveries. With this flair for drama and his rationale that germs could not appear supernaturally from boiled infusions, he answered the question, “Where did microbes come from if there was no spontaneous generation?” In a grand public lecture in 1864, he darkened the lecture room and projected a ray of light. Then he pointed to the dust particles in the light beam and exclaimed, “There is your source of germs – dust!” No microorganism, when exposed to a dust-free environment, can exist (recall the swan neck flask).

His fame continued with the discovery of microbes spoiling beer, milk, and wine, and attacking silkworms. With this discovery, he became a beacon in the fog by positing, “If microbes could make beer sick, could they do the same to humans?” Therefore, for the first time—if we know the cause of disease, germs or microbes, then we can better look for a cure. But his claim to fame did not stop there. With age, he was just getting started.

Later in his career, he turned to studying vaccines. His understanding of fermentation and disease confirmed his beliefs about disease and immunity through the activity of microbes. He saved the sheep of Europe by his creation of the anthrax vaccine. He was elevated to mythical status in the history of science with the creation of a vaccine for rabies in 1885.

At this point in human history, there is no record of any man or beast recovering from the germs of hydrophobia once the symptoms of rabies emerged. His obsession to solve this riddle came from the haunting cries of suffering children and the wails of mad dogs curdling the blood of his childhood neighbors. Here was a scientist who refused to shake people’s hands, but was willing to place his bearded face within inches of those fangs whose snap! meant a crazed death as he sucked up the froth into a tube during his hunt for the microbe of hydrophobia. Through his perseverance, observations, experimentations, and reasoning, he finally found a means to weaken this mysterious and unseen microbe. He created a plan of fourteen progressively stronger inoculations and confirmed immunity in his test animals against the most virulent unseen assassin. “It was an unheard-of triumph!” Once word got out, messages from all over the world came in begging him to use his vaccine on humans bitten by mad dogs. But it was not tested in humans. With his tendency for theatrics, he was tempted to inoculate himself with rabies and, knowing that it took two weeks for the neurologic manifestations to emerge, he would
give himself his 14 inoculations. It was then when the mother of a 9-year-old begged him to save her boy who was mangled by a mad dog. On July 6, 1885, the first injection of the attenuated microbes of hydrophobia was given into a human being. After 14 days, this boy completed the fourteen shots and went home to Alsace without a sign of this dreadful disease. Then Paris went mad and this chemist’s fame soared from the needs of those all over world. There was a sudden burst of generosity—bringing money in from every country on earth—for building a laboratory to conquer other deadly microbes.

At his 70th birthday in 1892, he was honored at the Sorbonne in Paris in the presence of Lister. His son had to speak for this feeble experimental scientist with these words,

“...Do not let yourselves be tainted by a deprecating and barren skepticism, do not let yourselves be discouraged by the sadness of certain hours which pass over nations. Live in the serene peace of laboratories and libraries. Say to yourselves first: “What have I done for my instruction?” And, as you gradually advance, “What have I done for my country?” Until the time comes when you may have the immense happiness of thinking that you have contributed in some way to the progress and good of humanity....”

So, are you sufficiently pasteurized?

If not, try this tidbit:

A milkman was making his deliveries and found a note attached to a customer’s door saying “I need 30 gallons of milk.” He knocked on the door and a beautiful blonde woman answered it.

“Is this a mistake?” the milkman asked.

“No,” she said, “I was watching a talk show and it said that bathing in milk will make you beautiful.”

“Really,” replied the milkman. “Do you want that pasteurized?”

The blonde replied, “No, just up to my waist.”

Disclosure statement:
The author has no conflicts of interest to disclose.

**CALL FOR NOMINATIONS TO ISHLT BOARD OF DIRECTORS**

Nominations to the ISHLT Board of Directors are being accepted through Monday, February 13, 2012. Information was distributed to all ISHLT members via email in mid-January.

For more information, please read the letter from John Dark, Immediate Past President and Chair of the ISHLT Nominating Committee available **HERE.**
JOHN WALLWORK RECEIVES HONOUR OF CBE

John Dark
Immediate Past President, ISHLT

When John Wallwork was born, the British Empire was still substantial and it was true that the “sun never set on the Union Flag.” Empires are now unfashionable—not even Americans want one—and the remnants for the UK are a few bits of rock jutting out of the lonelier parts of various oceans.

But twice a year, in a throwback to that distant time, individuals across the UK have their contribution to public life recognised by awards in the “Most Excellent Order of the British Empire.” One of the higher ranks is termed, “CBE” – not, in this case, Christians for Biblical Equality, or Commercial Bank of Ethiopia (or even Crabby But Efficient), but Commander of the Most Excellent Order of the British Empire.

This was the award made to ex-ISHLT President and recently retired transplant surgeon, John Wallwork, in January 2012. It recognises not only John’s significant contributions, but also those of his institution, Papworth Hospital, and indirectly, the whole of the heart and lung transplant community. John was a long-term supporter of the ISHLT, making a major impact on the Society over a 25 year career.

The award will be made in person by the Queen; for an ordinary, hard-working surgeon, a CBE is a particular achievement. Sting has one, as does Colin Firth and Helena Bonham Carter, but John is not as good looking as any of them.

Congratulations, John, from all of us in the world of transplantation.

INFECTIONOUS DISEASES COUNCIL REPORT

Lara Danziger-Isakov, MD, MPH
ID Council Chair

Coming off last year’s accomplishments, including publication of Monograph 5: Diagnosis and Management of Infectious Diseases in Cardiothoracic Transplantation and Mechanical Circulatory Support edited by Martha Mooney, Margaret Hannan and Shahid Husain, and the two consensus documents on infectious diseases definitions, the ID Council continues to be extremely productive. We maintain our collaborative work with several councils.

This fall, we spearheaded the ISHLT response to the proposed PHS Guidelines for Reducing Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) and worked with the leadership of ISHLT Academy to incorporate Infectious Diseases content to enhance this exciting educational opportunity. Stanley Martin leads ID topic contribution to LINKS monthly. Be on the lookout for new initiatives, including a survey of Infection Prevention Strategies in Mechanical Circulatory Support devices led by member Dr. Shimon Kusne. Further, our representatives to the Standards & Guidelines and Education Committees, Amparo Sole and Fernanda Silveira, are busy developing a new proposal to enhance infectious diseases resources in cardiothoracic transplantation.

The ID Council is excited to share more exciting ventures at the upcoming Annual Meeting – See you in Prague!!

Disclosure Statement:
The author has no conflicts of interest to disclose.
Once we had potent enough immunosuppression to allow heart and lung transplant recipients to leave the hospital after transplant and live to 1 year and beyond, the new problem—cytomegalovirus disease—was created. CMV also has direct and indirect effects that can cause a spectrum of illness and death.

The initial options for treatment and prevention were few. Intravenous ganciclovir was approved in June 1989 in the United States, oral ganciclovir followed in the early 90’s. Valganciclovir was approved for HIV retinitis in early 2001 which allowed its non-approved use in organ transplant. Approval in solid organ transplant occurred in 2002 in Europe and 2003 in the United States. The approved duration of prophylaxis was 100 days, carrying over the duration from the oral ganciclovir days. But the transplant community has not always used the prescribed 100 days.

Zuk et al reported on the responses they received to CMV Management Practices survey that was sent to 102 lung transplant programs. Of the 59 centers that responded the majority gave CMV prophylaxis to D+/r- patients for 3 – 6 months, with a small number giving prophylaxis for 1 year or indefinitely. In the D+/R+ and D-/R+ patients the overwhelming majority gave prophylaxis for 3 – 6 months. These durations are generally based on guidelines but the guidelines tend to be broad. The British Transplant Society recommends that for D+/R- lung transplant patients they should receive valganciclovir for 100 – 360 days, The Transplant Society Consensus guidelines recommend no less than 6 months of prophylaxis in the D+/R- patients and the American Society of Transplantation recommends 6 months with or without CMV IVIg.

Since valganciclovir is not approved for CMV prophylaxis in lung transplant, the lung transplant community has been left to define the optimal duration of prophylaxis. Zamora et al. showed that IV ganciclovir in combination CMV IVIg followed by valganciclovir for a period of 180, 275, and 365 days effectively decreased the incidence of CMV disease and infection compared to a control group that received acyclovir.

Palmer et al published their findings when looking at 3 months (followed by 9 months placebo) compared to 12 months prophylaxis in lung transplant patients at high (D+/R-) or intermediate risk (D+/R+ or D-/R+) for CMV. They found CMV disease eight times more often (4% vs. 23%, p<0.001) in the 3 month versus 12 month prophylaxis group. Often there is a concern that with prolonged prophylaxis we are merely delaying the CMV infection until after prophylaxis is complete. But the authors of this study showed that in the 6-month follow-up there was a low incidence of CMV disease in both groups, so CMV disease was not just delayed but avoided.

Although it is acknowledged that not all lung transplant patients who are CMV D+/R- may be able to tolerate 1 year of prophylaxis, perhaps it is time as a community to strive for 1 year of prophylaxis in CMV D+/R-. The intermediate risk (D+/R+, D-/R+) patients should be prolonged to 6 months though there has not been a study that examines the optimal duration for these patients.

Current guidelines for D+/R- heart transplant recipients recommend preemptive treatment or CMV prophylaxis for 3 – 6 months [2-4]. Our understanding of the causes of CAV are not definite, some research has been done examining the relationship between CMV and cardiac allograft vasculopathy. Potena et al, showed that there was less intimal thickening with universal prophylaxis versus a preemptive strategy but also documented that a substantial number of patients receiving either anti-CMV approach developed CMV infection (though significantly fewer prophylaxis patients had CMV disease compared to preemptive). Since CMV may contribute to the development or progression of CAV then preemptive treatment, with its allowance of viral replication before treatment, may not be the optimal approach to CMV prevention. Perhaps this finding should cause us to examine a prophylaxis strategy that will reduce the rate of CMV infection in order to decrease the impact that CMV may have on CAV progression. This may include extended prophylaxis and/or more aggressive late preemptive monitoring.

The future of CMV management may be a CMV vaccine. When studied in a kidney transplant population the vaccine attenuated CMV infections. Patients that received the vaccine and subsequently had CMV had a shorter duration of viremia and fewer days of ganciclovir therapy compared to patients that received a placebo.
Disclosure Statement:
The author has no conflicts of interest to disclose.

References:
Cytomegalovirus (CMV) remains the most common opportunistic infection after thoracic transplantation, and remains an incessant topic of heated discussions, from a brew of scientific evidence and passionate faith. Despite the increasing knowledge about CMV over the years, we still struggle with a number of questions. We are better at treating CMV disease since the dawn of heart and lung transplantation. However, we still fret over the long-term sequelae of CMV reactivation and disease. CMV, after all, has been associated with everything from an increased risk of diabetes to bronchiolitis obliterans syndrome (BOS) and allograft vasculopathy (CAV) to misplacing car keys or texting while driving (OK, those last ones are exaggerations... maybe...).

Prophylactic strategies are undoubtedly beneficial in a number of studies related to organ transplantation, and meta-analyses suggest a survival benefit of prophylaxis unattainable by pre-emptive strategies. Palmer et al’s important study in the Annals of Internal Medicine 2010 was the first multicenter, prospective, randomized, double-blind, comparative trial showing that lung transplant patients who received 12 months of valganciclovir prophylaxis had a greater freedom of CMV disease versus those who received a 3 month course. Similarly, in kidney transplantation, Humar reported that 6 months of prophylaxis was more efficacious than 3 months. Are these the final words on the subject? Some questions still linger and need addressing. Two members of the editorial board, “incidentally” involved in the CMV issue, have been interviewed to provide a unifying message.

S: Vincent and Luciano, the first point is: how long should patients receive prophylaxis? If 12 months of prophylaxis is superior to 3 months, then how about 6 months? How about 9 months? And how about longer?

L: The goal of anti-CMV strategies is not only to prevent CMV disease but also to minimize CMV subclinical replication to limit its “indirect” adverse consequences. However, CMV’s DNA is among the widest viral genomes ever sequenced. One of its most intriguing characteristics is that about 65% of the coded genes are not essential for replication, but instead have a regulatory effect on the host cell’s genome. Simply aiming for only one of the other 35% gene products (i.e. (val)ganciclovir inhibits just DNA polymerase), for either 3 or 12 months will not necessarily rid our patients of CMV. It would be more interesting to face the problem by acting on the interaction between CMV and the host with diagnostic and therapeutic tools. The real question to address is: what is the risk of CMV adverse events in my single patient? For example, a lung recipient is at higher risk of acute CMV disease than a heart recipient, a patient receiving thymoglobulin or any induction is at higher risk of one not receiving induction, and a patient not recovering his or her immunity may need a longer prophylaxis period than a patient recovering their immunity shortly after transplant. Thus, individualization of an anti-CMV approach may be more challenging, but seemingly more efficacious at determining duration of prophylaxis.

V: Before the availability of CMV prophylaxis, a number of lung recipients died of CMV induced ARDS within 2–12 weeks following lung transplantation. When ganciclovir became available via the HIV population and Merigan’s study in heart transplant recipients, lung recipients were placed on ganciclovir prophylaxis intravenously for 6 weeks. All this did to lung recipients was delay the identification of infection, disease and ARDS by that many weeks with nearly identical incidences. When Steve Duncan at Pittsburgh continued IV prophylaxis with ganciclovir up to 100 days, a similar delay of infection, disease and ARDS occurred. Associations with Gram negative respiratory infections and fungal infections were also observed. Also, consideration was given to restart ganciclovir intravenously, and later orally with the old poorly absorbed ganciclovir, and then eventually with the valine esterified formulation for better absorption. So instead of this on-off approach (a known means of promoting resistance), in 1995 the Ochsner lung transplantation program...
made a commitment to proceed with indefinite prophylaxis beginning with IV ganciclovir for 6 weeks, followed by thrice weekly until day 100, then the old oral agent indefinitely. There are many patients who remain on oral ganciclovir today, originally the old and now the new valine derivative by choice. They have witnessed the deaths of patients who seemingly have died as a consequence of discontinuing their ganciclovir primarily from cost.

Three index cases occurred within several months of each other. All patients had stopped their ganciclovir, developed a CMV respiratory event quickly, followed by the development of BOS within months of CMV, then death within a year. A total of 11 similar cases were identified.

For all patients remaining on indefinite prophylaxis (n = 116), only 2 percent have developed a CMV event, from either excess replication, CMV culture of lavage fluid or CMV disease. Interestingly, the 5 patients who developed CMV pneumonitis in the past 15 years were seronegative recipients to CMV of seronegative donors to CMV.

S: What do you think is the role of CMV IVIg in preventing CMV disease?

L: CMV IVIg is a very intriguing drug. It is likely that its action is more on the interaction between CMV and the immune system than on CMV itself. Unfortunately it has not been studied in any proper randomized study and it is unknown if the potential protective effect is mediated by IVIg in general or by CMV specificity. CMV IVIg may represent a useful resource in the effort to limit antiviral toxicity and provide some sort of immune modulation, especially in recipients with serological mismatch.

V: I agree, it seems to be most helpful in limiting the graft-related effect of the virus, more than the incidence of CMV disease itself (Valantine HA Transplantation 2001).

S: What, then, is the role of giving CMV prophylaxis indefinitely?

L: This approach is not justified. It may expose the patient to an excess of drug toxicity without a proven benefit. For example, the longer a patient receives antiviral drugs associated with a standard immunosuppression, which includes an antimetabolite, the greater the risk of leukopenia. At this point, what would you do? Reduce the antiviral drug, exposing the patient to the risk of viral resistance, or reduce the antimetabolite, exposing the patient to the risk of rejection?

V: I must admit, I disagree and I am biased. If herpes is forever, and immunosuppression is forever, then the risk of CMV (a herpes virus) reactivation, infection, disease and its long-term sequelae are always possible.

S: What are the real consequences of late onset CMV disease or reactivation in thoracic transplant patients?

L: Late onset CMV disease may be dangerous. The first reason is that it can be difficult to diagnose. The patient is often visited at long intervals and he or she may be seen in another hospital that may misdiagnose the syndrome. Then it may foster CMV indirect consequences on graft function, rendering useless the long period of time that he or she spent on prophylaxis. This may be a good reason for not prolonging universal prophylaxis beyond 3 months of post transplant follow-up and instead monitor for CMV viremia three to six months after the completion of prophylaxis. Monitoring for CMV specific immunity may help with treatment duration and identify patients at risk of developing late CMV disease.

V: The only way to avoid late infection is to continue prophylaxis indefinitely.

I leave you with these thoughts. If most of the adult population is immune to CMV (roughly 85%), think about how this group developed their immunity. Now consider who is at greater risk of CMV infection and damage to the allograft?

Lastly, the collateral benefits of this near-indefinite to indefinite prophylactic strategy are eliminating ARDS, reducing sudden death and preventing a slow suffocating death related to CMV-induced BOS. These benefits must be balanced with the risks of prolonged to indefinite (val)ganciclovir prophylaxis.

Well... is there a light in this fog? The message from our editorial board is not just what can be defined as a “unifying message”, but what reflects the real world of differing opinions in the clinical environment where most of our readers practice, with personal experiences, biases, truths, and untruths heavily influencing tough decisions at least as much as the published evidence. The key message, however, is that in 2012 CMV is still a threat and, despite
valganciclovir trials, an optimal strategy is yet to be determined. Thus, a watchful approach is recommended, regardless of the chosen strategy.

Until we have a better means of giving CMV immunity (vaccination) or treating or controlling CMV replication, we still will be wrestling the mad dog with what we should or shouldn’t do.

Let’s drink on it, have a beer!

Disclosure Statement:
The authors have no conflicts of interest to disclose.

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The specialty input of infectious diseases (ID) consultants has become a widely embraced feature of contemporary medical care. When a patient spikes a temperature or presents a possible infection, many caregivers do not hesitate to contact those with the expertise to suggest effective diagnostic approaches and therapeutic options. After all, studies have shown that having expert ID consultant care in cases of severe infections can reduce cost, duration of hospitalization, mortality, and increase a patient’s overall chance of cure.1-4

But what about the patient who has no known active infection? What role can an ID expert have in this clinical scenario? For a patient being evaluated for cardiothoracic transplantation, the work-up can be detailed, involving multiple procedures to see if the patient even qualifies as having sufficient end-organ disease. Other procedures such as cancer screening, extensive laboratory testing, and psychosocial evaluations may all be part of the process to ensure the patient can benefit from and handle a life-altering procedure with such a scarce and precious resource. Ensuring value over the long term, of course, is the goal. This is where your friendly neighborhood ID consultant can come in handy.

Screening assays for exposure to or infection with many agents have become more complicated with the advent of different molecular and cell-based assays. A case in point is the use of interferon-gamma release assays (IGRAs) for the detection of latent tuberculosis infection. These assays have different iterations with different degrees of clinical evidence to support their use compared to the classic tuberculin skin test approach. ID consultants’ familiarity with their sensitivity and overlap in detecting, or not detecting, other mycobacteria exposures can have a significant effect on patients about to undergo immunosuppression.

Delving into a patient’s past ID history allows an opportunity to uncover active infections, latent viruses, exposure to and colonization with drug-resistant pathogens, and to evaluate the role for decolonization or effective prophylaxis and monitoring in the post-transplant period. It can also allow clinicians the opportunity to predict what pathogens might be troublesome after the transplant process. Nowhere is this more important than in the patient presenting with severe infection. Empiric antibiotic therapy for septic transplant patients, when chosen incorrectly, can result in an increased risk of death.5

The other opportunity an ID evaluation pre-transplant can offer is the chance to administer needed vaccinations. Post-transplant, immune responses to routine vaccines may be diminished, and in the case of live viral vaccines, may be contraindicated altogether. In particular, updating influenza, tetanus, acellular pertussis, pneumococcal, hepatitis A and B, as well as many others, may all be indicated depending on the patient and region of the world in which he or she lives.

In today’s world, information abounds. For the modern-day cardiothoracic transplant recipient, the same can easily be said. Making sense of this information, and transforming it into the knowledge needed to treat and prevent infections, is a great investment in your patient’s future.

Disclosure Statement:
The author has no conflicts of interest to disclose.

References:
The spectrum of potential pathogens in the cardiothoracic transplant recipient (CT TX) is vast and has varied over time with the evolution of novel immunosuppressant regimens, and with the exposure to both prophylaxis regimens employed to avert infections and increasingly resistant nosocomial and community acquired bacteria. Successful clinical management of a bacterial infection in the CT TX includes appropriate empiric therapy at the time of presentation of an infectious disease followed by directed therapy for the identified pathogen(s). The carbapenems play a major role in empiric or pathogen directed therapy in these patients due to their broad spectrum of activity to pathogens resistant to other classes of antibiotics and also atypical pathogens that can infect this cohort of patients, like Listeria and Nocardia spp. Carbapenems are a class of broad-spectrum β-lactam antibiotics consisting of Invanz® (ertapenem), Primaxin® (imipenem/cilastatin), Merrem® (meropenem), and Doribax® (doripenem). This article aims to highlight the key differences that may influence therapeutic decisions by comparing and contrasting these carbapenems in terms of spectrum of activity, evolving resistance mechanisms, metabolism, pharmacokinetics/dynamics properties, differing tissue penetration capabilities and adverse effects of the individual drugs.

The carbapenems bind to penicillin-binding proteins (PBP), preventing bacterial cell wall synthesis. These agents are similar structurally and share similar spectrums of activity for the most part with some clinically important exceptions that will be discussed. Resistance to carbapenems can occur via several mechanisms. Pathogens may develop a reduced affinity of the target PBPs or an increased expression of efflux pump components. Gram negative bacteria may adapt a decreased permeability of the outer membrane due to diminished production of porins causing reduced bacterial uptake or may produce antibiotic-destroying enzymes like carbapenemases, metallo-β-lactamases and others.5-9

Gram Positive Organisms: All carbapenems have activity against Staphylococcus aureus (methicillin susceptible), penicillin sensitive Streptococcus pneumoniae, other aerobic and anaerobic Streptococcal spp, and Bacteroides fragilis. Enterococcus faecium and methicillin resistant Staphylococcus aureus are resistant to the carbapenems due to poor binding affinity for the necessary penicillin binding proteins.10 Imipenem/cilastatin is considered the most active of the group against gram positive organisms and is the only agent that should be used to simultaneously to treat Enterococcus faecalis (ampicillin susceptible) and other non-faecium species in a polymicrobial infection.12 Listeria1-4 and nocardia spp13-15-18 have demonstrated in vitro sensitivity and clinical successes are reported but no large clinical trials have been achieved nor likely will be due to infrequency of these diseases.17

Norcardia: All carbapenems have good to excellent activity against all strains of Nocardia, except Nocardia brasiliensis where 20-30% of isolates tested were sensitive to imipenem, and N. otitidiscaviarum where 0% of isolates were sensitive. Treatment recommendations for Nocardia asteroides, N. farcinica, N. nova, and N. transvalensis include ®imipenem/cilastatin (which has the most evidence for treatment of nocardiosiss14-17), or meropenem in addition to 1 or 2 other classes of potentially active drugs empirically until the sensitivities of the specific Nocardia spp pathogen are available.17 Meropenem may be the preferred carbapenem over imipenem with a much lower seizure threshold in this disease that may be associated with central nervous system (CNS) involvement.12,14-18 Doripenem, with little CNS penetration with an intact blood brain barrier (BBB) and no data demonstrating CNS penetration with an inflamed BBB, should be avoided in any infectious process involving the CNS.19 A CT TX presenting later than 30 days after transplantation with a pneumonia should consider Nocardia in the differential of possible pathogens and CNS penetration of the empiric therapeutic regimen is warranted till the definitive diagnosis is known.

Gram Negative Organisms: The carbapenem class of drugs until recently has maintained broad gram negative antimicrobial activity due to their stability against most β-lactamases produced by gram negative bacteria, including extended spectrum beta lactamases (ESBL) and Amp-C β-lactamases.5-6 Carbapenem resistance has been increasingly detected due to the production of carbapenem hydrolyzing enzymes in the Enterobacteriaceas spp (carbapenem

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CARBAPENEM’S ROLE IN EMPIRIC AND DIRECTED THERAPY FOR BACTERIAL INFECTIONS IN CARDIOTHORACIC TRANSPLANTATION: ARE ALL CARBAPENEMS CREATED EQUAL?

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The spectrum of potential pathogens in the cardiothoracic transplant recipient (CT TX) is vast and has varied over time with the evolution of novel immunosuppressant regimens, and with the exposure to both prophylaxis regimens employed to avert infections and increasingly resistant nosocomial and community acquired bacteria. Successful clinical management of a bacterial infection in the CT TX includes appropriate empiric therapy at the time of presentation of an infectious disease followed by directed therapy for the identified pathogen(s). The carbapenems play a major role in empiric or pathogen directed therapy in these patients due to their broad spectrum of activity to pathogens resistant to other classes of antibiotics and also atypical pathogens that can infect this cohort of patients, like Listeria and Nocardia spp. Carbapenems are a class of broad-spectrum β-lactam antibiotics consisting of Invanz® (ertapenem), Primaxin® (imipenem/cilastatin), Merrem® (meropenem), and Doribax® (doripenem). This article aims to highlight the key differences that may influence therapeutic decisions by comparing and contrasting these carbapenems in terms of spectrum of activity, evolving resistance mechanisms, metabolism, pharmacokinetics/dynamics properties, differing tissue penetration capabilities and adverse effects of the individual drugs.

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resistant Enterobacteriaceae or CRE) and other Gram-negative organisms. In the United States, according to the National Healthcare Safety Network (NHSN) 2006-2007 survey, E. coli with CRE were 4% and Klebsiella spp with CRE were 10.8% of isolates associated with certain device related infections. Different regions of the world vary greatly in the percentage of carbapenem resistant isolates that are in the endemic flora.

Excellent activity persists for the Enterobacteriaceae without CRE, E. coli (including those producing extended spectrum β-lactamas (ESBL)), Klebsiella spp (including ESBL), Haemophilus influenzae (β-lactamases-and non-β-lactamases-producing), Neisseria meningitidis, Morganella spp, Enterobacter spp, Citrobacter spp, Salmonella spp, Shigella spp, Proteus mirabilis, and with the exception of ertapenem, Pseudomonas aeruginosa and Acinetobacter spp. Compared to the other carbapenems, meropenem and doripenem have similar susceptibility patterns and slightly lower MICs against many of the gram negative bacteria in published series.

Gram Negative Pseudomonas: Imipenem/cilastatin, meropenem and doripenem are the anti-pseudomonal carbapenems. Ertapenem does not have anti-pseudomonal activity. Carbapenem resistance among Pseudomonas aeruginosa isolates is variable within this class of drugs. Pseudomonas can become resistant to imipenem/cilastatin with the loss of the OprD porin, while meropenem and doripenem require both the upregulation of the MexA-MexB-OprM multidrug efflux pump combined with the loss of OprD. Imipenem is not affected by upregulation of MexA-MexB-OprM, as it is not subject to efflux. While uncommon, these varied mechanisms of resistance to carbapenems allow for certain pseudomonal isolates to have different MICs to imipenem/cilastatin vs. meropenem/doripenem. The clinical pearl is that if pseudomonas is the suspected pathogen prior to the MICs becoming available, meropenem or doripenem would be the most likely carbapenem to be active against the pathogen of concern. If CNS involvement is suspected in the disease, doripenem should be avoided as previously discussed.

Metabolism: Imipenem differs from the other carbapenems in that is it extensively metabolized by renal dehydropeptidase-1, and as such, is formulated with cilastatin, which inhibits this enzyme. All carbapenems are renally excreted (70-80%) and all require renal dose adjustments, with ertapenem having the highest protein binding and longest half-life allowing for once daily dosing.

Pharmacokinetics/dynamics properties: The efficacy of the carbapenems, like other β-lactams, is associated with the time above the MIC, where a percentage of the dosing interval during which the concentration is greater than the MIC (T>MIC) of approximately 20% is considered bacteriostatic and 40% is considered bactericidal. Imipenem, meropenem, and doripenem, the anti-pseudomonal carbapenems, easily achieve this 40% T>MIC target against a Pseudomonas isolate with an MIC of 1 mcg/ml using standard dosing. However, against a psuedomonal isolate with an MIC at the respective breakpoints (4mcg/ml for imipenem and meropenem, 2mcg/ml doripenem) the probability of achieving the T>MIC target of 40% is dependent on the infusion time using standard doses/frequencies. The ability to achieve these targets decreases as an organism’s MIC increases and as the infusion time decreases. This is evidence that the choice of a carbapenem with a more favorable MIC (vs. one where the MIC is at the break-point of susceptibilty) and administration over an extended infusion time may be beneficial.

Tissue Penetration: Carbapenems are thought to penetrate a variety of fluids/tissues. Only meropenem is approved for meningitis treatment. Imipenem’s safety for CNS infections has not been established and incidence of seizures is a concern. Imipenem is recommended for treatment of serious infections caused by susceptible strains of microorganisms. All carbapenems have approved indications for polymicrobial intra-abdominal infections and complicated urinary tract infections.

The carbapenems are useful for their broad spectrum coverage as empiric therapy and are powerful therapeutic agents as directed therapy for atypical pathogens or resistant nosocomial or community acquired susceptible pathogens. It is imperative that we safeguard the efficacy of this class of antibiotics by preventing the spread of the newly resistant strains of pathogens with effective infection control measures globally.

Disclosure Statement:
The authors have no conflicts of interest to disclose.

References


Since its first description as a cause of antibiotic-associated colitis in 1978, Clostridium difficile has become the most common cause of hospital-acquired infectious diarrhea. This anaerobic, spore-forming bacterium infects the lining of the colon, and causes damage to the colon by release of toxins, toxin A and toxin B. The clinical manifestations can range from mild diarrhea to colitis, toxic megacolon, and complications such as colonic perforation and death. In recent years, there have been dramatic increases in the incidence and severity of C. difficile infection (CDI) as well as increasing difficulty in successfully treating this infection. In fact, almost 1/3 of patients who are treated for CDI have repeated episodes of infection. The recent rise in the occurrence and severity of CDI has largely been attributed to the emergence of a more virulent, hyper-toxin-producing and fluoroquinolone antibiotic-resistant strains of C. difficile, BI/NAP1/027.

CDI is an all too frequent complication of cardiothoracic transplantation—up to 15% of heart recipients and 7-31% of lung recipients are affected. CDI usually occurs during the first 3 months following transplant, but heart and lung recipients remain at risk for the infection even years after transplant. This is not surprising, given the fact that transplant patients inherently have many risks for CDI. Foremost, transplant patients are repeatedly treated with broad-spectrum antibiotics, resulting in drastic changes in gut flora, and allowing C. difficile to flourish in the gastrointestinal tract. Other risks for CDI common in transplant patients include the use of proton pump inhibitors and, often, prolonged or repeated hospital stays. Finally, cardiothoracic transplant patients are uniquely at risk for CDI because of hypogammaglobulinemia and the use of immunosuppressive medications.

Recurrent CDI is very problematic in transplant patients who may have a difficult time in clearing the infection because of defective immune responses, especially the inability to make antitoxin-neutralizing antibodies. Additionally, because of prolonged and repeated exposure to antibiotics, it is difficult to re-establish the normal gut flora of transplant patients and this, too, makes it more difficult to eradicate C. difficile from the gastrointestinal tract.

Diarrhea is a common complaint in heart and lung transplant recipients, and because it has numerous causes, including immunosuppressive medications, early recognition of CDI can be a diagnostic challenge in this population. Currently available laboratory detection methods are hampered by suboptimal accuracy. Most laboratories use tests to detect toxin production in stool specimens with either a cytotoxicity assay performed in tissue culture or, most commonly, with enzyme immunoassays (EIA) for toxins A and B. For cost-effectiveness, some laboratories have adopted a 2-step testing strategy involving rapid screening with an EIA test for C. difficile common antigen, glutamate dehydrogenase (GDH), followed by a toxin assay for GDH-positive specimens. Polymerase chain reaction (PCR) detection of C. difficile is now available and may ultimately prove to be the most sensitive and specific test for CDI. To improve diagnostic accuracy of any of these tests, only non-formed stool should be submitted for testing. Importantly, submitting multiple fecal specimens for testing only adds to the cost of testing without improving the diagnostic yield.

A vital component of successful CDI treatment is discontinuation of inciting antibiotics whenever possible. The first line therapy for mild to moderate CDI is metronidazole (500 mg 3 times daily for 10-14 days). For severe CDI, oral vancomycin (125 mg 4 times daily for 10-14 days) is the preferred agent. With severe CDI complicated by ileus, increased doses of vancomycin (up to 500 mg 4 times daily), Intravenous (IV) metronidazole, and vancomycin enemas can be considered. For recurrent CDI, re-treatment with either metronidazole or vancomycin is recommended, but for repeated recurrences, vancomycin with a tapering or pulse dose schedule can be effective. Other therapies such as IV immunoglobulin, oral vancomycin followed by rifaximin, and nitazoxinide are not well studied. Probiotics, Saccharomyces boulardii, and fecal transplantation have been used for recurrent CDI but cannot be recommended for use in transplant patients due to the potential infection hazards of these therapies.
Fidaxomicin, a macrolide antibiotic with narrow activity specifically for C. difficile, represents a new therapeutic option for CDI. In clinical studies, fidoxamicin had CDI cure rates comparable to vancomycin, and less recurrences of CDI occurred with fidaxomicin (15% v. 25%), but recurrence rates were similar for both drugs for infections with strain BI/NAP1/027. Immunotherapeutics, such as monoclonal antibody directed against toxin B, are in development and offer a promising new avenue for the treatment of CDI.

Prevention is the best weapon against CDI. C. difficile is spread by direct contact with patients with CDI, healthcare workers that carry C. difficile on their hands, or a contaminated environment.

Efforts to eliminate transmission of C. difficile in the hospital include meticulous hand washing, contact precautions such as the use of glove and gowns, and disinfection of the environment with hypochlorite. Finally, the most easily correctable risk factor for CDI in the transplant population is antibiotic use. As a transplant community, we can significantly reduce the risk of CDI in our patients by reducing the frequency and duration of antibiotic courses in our patients.

Disclosure Statement:
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VAD REIMBURSEMENT SESSION

ISHLT will be conducting an educational session at the Annual Meeting in April in Prague regarding how to accommodate the recently implemented changes to MCS billing by CMS. This session will take place during the MCS Council Meeting. Look for details on date/time/location of the MCS Council Meeting in the 2012 April Links issue.

The US Center for Medicare and Medicaid Services (CMS) has proposed significant changes in reimbursement for transplant and mechanical circulatory support procedures. The ISHLT supports advocacy of its membership as well as for patient care and is developing a forum to educate US surgeons and HF cardiologists of these regulatory changes and of the requirements necessary to capture reimbursement of postoperative care at this year’s 2012 ISHLT Scientific Meeting in Prague. In the spirit of the ISHLT, we will also devote a portion of the session to any new major MCS reimbursement issues outside of the US.

The following changes have been proposed by CMS:

- A reduction in reimbursement for VAD implant procedures but allowances for reimbursement of VAD-related “critical care”.
- Effective Jan. 1, 2012, the physician payment policy for Ventricular Assist Device removal procedures will change. Payment values will be reduced and no longer include reimbursement for in-hospital and out-patient evaluation and management services. Payments could be reduced dramatically - up to 30 percent - unless you prepare for this change.

If you do VAD procedures, you are providing a substantial amount of critical care as well as in-patient and out-patient care, which are currently reimbursed automatically. However with these changes, those services must be processed in an itemized fashion for each patient. Accurate documentation of services provided requires surgical insight and is the surgeon’s responsibility, and accurate documentation is critical for correct coding and ultimately correct reimbursement.
Invasive fungal infections are associated with significant morbidity and mortality in transplant recipients. Not only are transplant recipients more susceptible to these infections due to their immunocompromised state, but treatment itself can pose its own challenges. Azole antifungals are frequently chosen to prevent or treat these infections. Concomitant use of azole antifungals and immunosuppressants such as calcineurin inhibitors (CNI) and mammalian target of rapamycin (mTOR) inhibitors can result in clinically significant drug interactions since azole antifungals inhibit cytochrome P450 (CYP450) enzymes that metabolize these immunosuppressants. Anticipation of these interactions enables clinicians to use these agents together and minimize toxicities and/or supratherapeutic immunosuppressant concentrations when initiating azole antifungal therapy. When the azole antifungal is discontinued, awareness of the drug-drug interactions can prevent sub-therapeutic immunosuppressant concentrations. In this article, we offer strategies for managing these clinically meaningful drug-drug interactions.

The CYP450 enzyme system, particularly the 3A4 isozyme, is responsible for the oxidation of both CNI and mTOR inhibitors. Importantly, azole antifungal agents inhibit CYP450 3A4 and inhibit immunosuppressant metabolism. Another key component of these interactions involves P-glycoprotein (P-gp). As an active transport protein, P-gp has the potential to affect drug bioavailability by either decreasing absorption or increasing elimination. Both CYP450 enzymes and P-gp are found within the gastrointestinal tract and the liver. The presence of these elimination pathways creates a hurdle for immunosuppressants after oral administration as they are eliminated in the gut prior to systemic absorption. The process of drug elimination in the gut prior to systemic absorption is termed first pass metabolism. Inhibiting these proteins in the gut results in more immunosuppressant being available for systemic absorption.

The full effect of inhibition for both CYP450 and P-gp is typically seen within the first week after the azole antifungal is initiated. Therefore, monitoring of cyclosporine, tacrolimus, sirolimus, and everolimus levels 2-3 times per week for 1-2 weeks is recommended. Upon discontinuation of the azole antifungal agent, the effect can last 7-10 days depending on the half-life of the offending agent, the relative degree of 3A4 inhibition, and the dose of the azole.

Higher doses of azole antifungal agents may be associated with more clinically significant drug-drug interactions. Thus, treatment doses are typically more problematic than prophylactic doses. For example, fifty milligrams of fluconazole did not significantly affect tacrolimus concentrations in kidney transplant recipients, while higher doses significantly inhibit CYP450. Table 1 (below) provides preemptive dosing strategies based upon the available literature and prescribing information for patients who currently maintain stable trough concentrations of CNI and mTOR inhibitors. As new agents become available, awareness of the underlying mechanisms involved in these drug-drug interactions allow for judicious use of immunosuppressants and azole antifungals concomitantly. Of note, no clinically significant drug interactions exist among antiproliferatives, polyclonal, or monoclonal antibodies when used concomitantly with azole antifungal agents. Steroids have been known to exacerbate certain fungal infections, but no drug-drug interactions are described in the literature.

In the perioperative period, antifungal prophylaxis is commonly initiated at the same time as immunosuppression, when patients have not yet achieved therapeutic immunosuppressant concentrations. Judicious monitoring of immunosuppressant concentrations is warranted in the perioperative period. Current guidelines indicate clotrimazole troches are one of the more common agents used to prevent mucocutaneous candidiasis. Given the limited evidence regarding interactions between immunosuppressants and clotrimazole, routine monitoring of immunosuppressant concentrations is crucial, as the effects of the enzymatic inhibition may not be recognized until discontinuation of the prophylaxis. This principle holds true for other azole antifungals as well. Dosing strategies are offered for initiation of azole therapy, however upon discontinuation of the azole, monitoring of immunosuppressant plasma concentrations must guide clinicians to appropriate dose adjustments. Therefore, we recommend obtaining CNI and mTOR inhibitor concentrations 2-3 times per week for a minimum of 2 weeks following discontinuation of azole antifungal therapy to
minimize the chance of subtherapeutic immunosuppressant concentrations and subsequent rejection. Based upon dosage adjustments and interpatient variability, additional monitoring may be warranted.5

Predicting drug-drug interactions can be very challenging depending on the degree of inhibition of metabolic enzymes when azole therapy is initiated. The recommendations provided here offer preemptive dosing strategies for immunosuppressants at the initiation of azole therapy as well as monitoring considerations upon discontinuation of the azole.

Table 1. Initial recommended dosing strategies of concomitant azole antifungal agents and immunosuppressants when initiating azole antifungal agents and stable immunosuppressant concentrations have been achieved.1,5,9-25

<table>
<thead>
<tr>
<th>Azole Antifungal Agent</th>
<th>Calcineurin Inhibitors</th>
<th>Mammalian Target of Ramapycin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease Cyclosporine Dose</td>
<td>Decrease Tacrolimus Dose</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>No data</td>
<td>33-50 %</td>
</tr>
<tr>
<td>Fluconazole (&gt;150mg/day)a</td>
<td>50 %</td>
<td>40-50 %</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>50-60 %</td>
<td>50-60 %</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>50-67 %</td>
<td>50-60 %</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>25 %</td>
<td>67-75 %</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>50 %</td>
<td>67 %</td>
</tr>
</tbody>
</table>

a. Consider judicious monitoring of immunosuppressant concentrations if utilizing fluconazole >100mg daily
b. Concomitant administration not recommended by package label without sufficient published data to support concomitant use
c. Concomitant administration contraindicated according to package label without sufficient published data to support concomitant use
d. Concomitant administration contraindicated according to package label with published literature to guide management of drug-drug interaction

Disclosure Statement
The authors have no conflicts of interest to disclose.

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13. NEORAL® (cyclosporine-modified) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2005.


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During the time of the Great War, a young Scottish physician, serving as a medical officer with the British army, observed many deaths of soldiers from the helpless inability to rid the bacteria hidden within the crevices of their jagged wounds. It was not because he wasn’t trying, but rather his attempts at cleansing the wounds with antiseptic chemicals were rarely useful. He began to reason that the best way to render the soldier’s wounds germ free would be to inject antiseptic into his blood, but this seemed to be a dangerous proposition. Such an approach was known to be poisonous to both bacteria and people, and he published that antiseptics were killing more soldiers than the infection itself during the War to end all Wars.

After November 11, 1918, he returned to a civilian position at St Mary’s Hospital in London as a researcher. He was on a mission to find a substance harmless to humans but deadly to bacteria with a goal to inject a safe antiseptic into patients’ bloodstream. He worked diligently and methodically with failure after failure in his search of such a chemical.

On a hunch, he decided to test the effect of his own nasal secretions on bacteria. He discovered that his own nasal mucus and eventually tears and saliva possessed some bacteria-killing agent that destroyed most cultures of bacteria in Petri dishes. He further discovered that laboratory mice, domestic animals, and every species of fish he caught produced this same substance capable of killing most bacteria. This substance, harmless to humans, he named lysozyme (first line of innate immunity).

In late summer of 1928, disgruntled after finding that some mould had ruined some of his bacteria cultures, he observed perchance that no germs were growing in a circle around a blob of mould in the culture dish of *Staphylococcus aureus*. The yellow bacterial colonies had been polluted by green mould. Around the mold, the bacteria lost their healthy golden color and were dissolving into drops of clear fluid. Fleming then swabbed some mould of this culture dish and transferred it to a clean dish. He then cultivated this mould and filtered a liquid he called “mould juice.” He later found that this juice killed many deadly bacteria without harming human blood cells. When injected in mice, it did no harm. The mould turned out to be a rare strain of the species, *Penicillium notatum*.

Next, he launched a quest to determine if all species of mould produced this juice. He cultivated mould from dirt, tainted cheeses, rotten vegetables, and asked his friends, “If any of you chaps have a pair of mouldy old shoes, I’d like to have them.” He discovered that none of these different sources of mould produced a significant amount of “mould juice.” Then he realized his great fortune of having an airborne mould spore floating into his laboratory through an open window and perchance landing on his culture plates. However, he was much less fortunate when he tested this juice in human volunteers. It did not harm anyone, nor did the juice cure anyone’s infection. He noted that this mould juice, penicillin, killed all bacteria in a culture dish, but proved ineffective in human patients. In 1929, he published his disappointing results and abandoned his work with penicillin.

At Oxford University in 1938, Howard Walter Florey read and studied these earlier works published about *Penicillium notatum*. Florey and other scientists identified the active ingredient in penicillin and produced large quantities to cure sick mice. During a lull in the violence of World War II, the diligent Scottish physician traveled from London to Oxford to meet Florey and Ernst Boris Chain. It wasn’t until 1942 when the Scot learned that Florey’s team purified enough penicillin to successfully treat a human patient.

The most noble and notable deed lost and veiled by the knighting of this Scot in 1944 and the jointly awarding of the Nobel Prize in Medicine in 1945 to Sir Alexander Fleming, Ernst Boris Chain, and Sir Howard Walter Florey was when Fleming declined to claim a patent on penicillin. This chivalrous generosity to mankind speedily allowed the mass production of penicillin by every pharmaceutical manufacturer in England and the United States to freely profit and provide the most useful lifesaving drug the world had ever seen.

Disclosure Statement:
The author has no conflicts of interest to disclose.
Infectious Diseases will be significantly highlighted during a variety of symposia during the meeting. In the session, CMV & Beyond, we will highlight emerging viruses in thoracic transplantation as well as discuss developing issues with cytomegalovirus. Bad Bugs –What Can We Do? includes discussions of the impact of multi-drug resistant gram negative organisms, VRE and MRSA and Clostridium difficile, with a focus on prevention.

Infectious diseases will also be woven into sessions sponsored by other councils, including talks on infections in Mechanical Circulatory Support and in transplant candidates with Cystic Fibrosis.

Finally, we will have the opportunity to evaluate the Risky Business of Transplantation, focusing on candidates and donors with chronic hepatitis and history of international travel.

Members of the new Pharmacy and Pharmacology Council will be featured Thursday morning in the inaugural symposium in a series entitled, A Lifecycle Journey in Advanced Heart Failure and Transplantation, sponsored by the ISHLT Pharmacy and Pharmacology Council. This series, focusing on therapeutic aspects that uniquely involve emerging or established knowledge in the pharmacology and pharmacy, envisions using an enduring case to create a panel facilitated and audience supported best practice-based discussion at predefined key “journey intervals.” In this session the focus will be on the life-cycle of Advanced Heart Failure and Cardiac Transplantation with special emphasis on the “journey points” of Mechanical Circulatory Support and anticoagulation, post-transplant development of Antibody Mediated Rejection and late complications that demand innovative immunosuppressive strategies.
The ISHLT Abramson-Imhoff Links Travel Awards, funded in part by the generous support from Mrs. Sue Abramson (Birmingham, Alabama, USA) and Mr. Larry Imhoff (La Place, Louisiana, USA), have been established to contribute to the development of our future leaders which include physicians, nurses, and other health care professionals within the ISHLT. Our intent is to support their evolving expertise in investigation, communication, and dissemination of new ideas for the betterment of patients with failing lungs and/or a failing heart including such conditions as pulmonary fibrosis, cystic fibrosis, emphysema, pulmonary hypertension, and the various heart diseases.

Those eligible for such support from this travel fund must fulfill the following criteria:

1. Any healthcare professional including nurses, nurse coordinators, social workers, pharmacists, therapists, dietitians and early career physicians are eligible and must be a member of the ISHLT regardless of duration in their career.

2. An imposed restriction on physicians is that they must be in their Early Career – within 7 years of their training, Assistant Professor equivalent, or junior faculty level.

3. Individuals must display some form of research interest, basic, clinical, translational or outcomes investigations or at a minimum display some skill in journalism best exemplified by their contributions to the Links Newsletter engendering fresh and creative ideas.

In summary, a young investigator, budding scientist, leader, or skillful and thoughtful writer, who shows an interest in research of some sort with an uncanny ability to think creatively enough to share their ideas through the Links, would be eligible to receive the maximum support from this fund to help offset the costs to attend the Annual Meeting. Smaller stipends will also be available for others.

With this fund, the ISHLT will be able to lend a hand to our future leaders with creative writing skills in sustaining our Society by keeping us in the vanguard of managing such complicated patients in perpetuity.

Each year, the winners will be selected by: Dr Vincent Valentine (custodian of the fund); the ISHLT Executive Director; the ISHLT President; the ISHLT Program Chair; the Links Editor; and the Links Managing Editor.

As this year marked the first bestowment of these awards, the recipients were selected by the Editorial Staff and approved by the ISHLT Board of Directors. Please join me in congratulating the winners of the 2012 ISHLT Abramson-Imhoff Links Travel Awards.

**Writer of the Year - $4,000.00**

**Tereza Martinu, MD**

Tantalizing us with her monthly depictions of the rich culture and history of Prague, Dr. Martinu (Duke University Medical Center, USA) has all of us prepared for our trip to Prague this April. We owe her an enormous debt of gratitude for the wealth of knowledge she has shared with us about her home country. Currently, Dr. Martinu is an Associate Editor (Pulmonary) for the Links Newsletter, a member of the Scientific Councils on Pulmonary Transplantation, Basic Science & Translational Research, and Junior Faculty & Trainees, and served as an Abstract Reviewer this year.

**First Runner-Up - $1,000.00**

Two individuals were selected to receive this award:

**Stanley I Martin, MD**

As leader of the Communications Workforce of the ISHLT Infectious Diseases Council, Dr. Martin (The Ohio State University Medical Center, USA) has gone above and beyond the call of duty by contributing articles for the June, July, August, September, and October 2011 issues. He has also been instrumental in helping to gather, as well as write and collaborate, quality ID content for the February 2012 issue. Dr. Martin is an Associate Editor (Infectious Diseases) of the Links Newsletter, and served as an Abstract Reviewer this year.

**Luciano Potena, MD, PhD**

Dr. Potena has contributed several articles for the Links Newsletters, including a piece on AMR in July 2011, and an in-depth article...
“Travel Awards...” Continued

interviewing 6 transplant and VAD experts in October 2011. From
the University of Bologna (Italy), Dr. Potena is a member of the ISHLT
2012 Annual Program Committee, collaborating with several other
ISHLT members in the Heart category to put together a very exciting
scientific program in Prague. He is an active member of the Scientific
Councils on Heart Failure & Transplant Medicine, Infectious Diseases,
and Junior Faculty and Trainees. He is also a member of the Links
International Correspondents Board.

Honorable Mention - $500.00

Five individuals were selected to receive this award:

Nancy P Blumenthal, CRNP and
Bronwyn J Levvey, RN

Both Nancy Blumenthal (Univ of Pennsylvania
Medical Center, USA) and Bronwyn Levvey
(Alfred Hospital, Australia) are to be commended
for their outstanding job in soliciting, motivating,
gathering, and editing all of the content for the
January 2012 issue which focused on Nursing,
Health Sciences and Allied Health. With very
little guidance, they were able to develop the
January issue into a masterful work of literary
art to usher in the New Year for the heart and
lung transplant community. Currently, Nancy
is Chair of the Nursing, Health Sciences and
Allied Health (NHSaH) Council and is an Associate Editor (Nursing)
of the Links Newsletter. Bronwyn is the Communications Workforce
Leader of the NHSaH Council, a member of the 2012 Annual Program
Committee, and a member of the Pulmonary Transplantation Council.
She is also a member of the Links International Correspondents
Board.

Stavros G Drakos, MD

Dr. Drakos (Univ of Utah School of Medicine,
USA) contributed a very intensive two-part
report on the Heart Transplantation Society
of America’s 15th Annual Scientific Meeting,
which appeared in both the December 2011 and
January 2012 issues. Dr. Drakos is an Associate
Editor (Cardiology) of the Links Newsletter, and a member of the
Heart Failure & Transplant Medicine Council and the Mechanical
Circulatory Support Council. He also served as an Abstract Reviewer
this year.

Daniel F Dilling, MD

Dr. Dilling (Loyola Univ Medical Center, USA)
has been instrumental in orchestrating and
guiding writers to contribute content for the
forthcoming March 2012 issue of the Links
Newsletter, focusing on Junior Faculty and
Trainees. His eagerness and initiative in tackling
this time-consuming job have not gone unnoticed! Dr. Dilling is the
current Chair of the Junior Faculty and Trainees Council, as well
as a member of the Pulmonary Transplantation Council. He is an
Associate Editor of the Links Newsletter (Junior Faculty & Trainees),
served on the 2011 Program Committee, and also served as an
Abstract Reviewer this year.

Javier Carbone, MD, PhD

Dr. Carbone (Gregorio Maranon Hospital,
Spain) has contributed articles for the June, July,
and September 2011 issues. His unsolicited
motivation and assistance proved useful and
invaluable for the few issues of Volume 3 of the
Links. He is a member of the Links International Correspondents
Board as well as the Heart Failure & Transplant
Medicine Council and Infectious Diseases Council. Dr. Carbone also
served as an Abstract Reviewer this year.
Antimicrobial chemoprophylaxis is becoming increasingly important in the setting of advanced immunosuppressants, extended criteria donors, and a progressively older recipient population. Common targets of antimicrobial chemoprophylaxis include: Pneumocystis, Cytomegalovirus, and various fungi.

Anti-Pneumocystis prophylaxis continues to be recommended for all transplant recipients. Duration ranges from six months to lifelong, depending upon organ type and risk factors. Trimethoprim-sulfamethoxazole (TMP/SMX) continues to be the drug of choice as it is readily available, well tolerated, and has great breadth of coverage, including toxoplasma, listeria, and many respiratory and gastrointestinal microbes. Effective TMP/SMX prophylaxis regimens vary from a single-strength tablet daily to a double strength tablet once or twice daily, two to three times weekly. The most common side effects of TMP/SMX include gastrointestinal upset (nausea, vomiting, loss of appetite) and rash or urticaria. Bone marrow suppression, Stevens-Johnson syndrome, hepatitis, and interstitial nephritis are also possible. TMP and SMX are metabolized by the liver and excreted via the kidneys. SMX is an inhibitor of CYP450 2C9 and will potentiate the effects of drugs such as warfarin. TMP inhibits renal tubular secretion of potassium and creatinine, creating laboratory abnormalities that may not be indicative of true renal function. However, increased half-life and/or reduced clearance of TMP/SMX in the elderly and those with reduced renal function have been shown, in which cases dose reductions may be necessary.

Second-line agents for PCP prophylaxis include dapsone, atovaquone, and inhaled pentamidine. Dapsone is associated with hemolytic anemia and methemoglobinemia, and patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency care at increased risk. While dapsone does not contain the classic sulfonamide moiety, it does contain an arylamine group and should be avoided in patients experiencing anaphylaxis or other severe reactions to sulfonamides. Atovaquone is only available as a suspension and should be given with food to enhance absorption. The most common adverse effects seen with atovaquone include rash and gastrointestinal upset (diarrhea, nausea, vomiting, abdominal pain). Atovaquone is minimally metabolized and primarily excreted via feces, so dose adjustments are not generally required.

Inhaled pentamidine therapy is usually last-line due to special administration requirements and reduced effectiveness compared to TMP/SMX and dapsone.

Cytomegalovirus (CMV) infection post-transplantation remains a pervasive concern. Oral valganciclovir (VGCV), oral ganciclovir (GCV), and intravenous GCV are the recommended agents for CMV prophylaxis. Duration of universal prophylaxis for CMV generally ranges from three months to one year. VGCV is the valine ester prodrug of GCV; both inhibit viral DNA synthesis. VGCV 900mg orally provides systemic exposure similar to 5mg/kg IV GCV. VGCV provides the benefits of increased oral bioavailability, reduced pill burden, and reduced dosing frequency over oral GCV. VGCV and GCV require dose adjustment for renal dysfunction. VGCV is not recommended in patients on hemodialysis, and GCV should be used in these patients. Furthermore, dosing in pediatric patients should never exceed the normal adult dose. VGCV and GCV are associated with diarrhea, tremor, increased serum creatinine, and may induce significant myelosuppression (anemia, thrombocytopenia, neutropenia). VGCV should be given with food to enhance absorption. Pharmacodynamic interactions include increased risk of seizure when used with imipenem and increased risk of myelosuppression with drugs like mycophenolate mofetil or TMP. Late-onset CMV in the setting of prolonged prophylaxis is an evolving issues that will benefit from further study.

Antifungal prophylaxis varies depending upon transplant organ and center. Heart transplant recipients with endemic fungal exposure often receive antifungal prophylaxis. Aspergillus infection is of particular concern in the lung transplant population, and thus voriconazole and/or amphotericin are frequently utilized in this group. Duration of prophylaxis varies widely from two weeks to lifelong. Amphotericin B and its various lipid formulations have a broad spectrum of activity, binding ergosterol in fungal cell membranes, altering permeability and ultimately leading to cell death. Inhaled amphotericin B or lipid complex amphotericin B are both used prophylactically in lung transplant recipients. Inhaled amphotericin regimens vary from 6-30mg/day of amphotericin B to 50mg lipid complex amphotericin B once weekly. Systemic exposure with inhaled amphotericin is limited, thus limiting the risk of nephrotoxicity. However, cough, bronchospasm, and nausea are frequently observed.
Systemic antifungal prophylaxis with fluconazole, voriconazole, or itraconazole is also used. Azoles damage fungal cell walls by disrupting ergosterol biosynthesis. Voriconazole, with or without inhaled amphotericin, is often the drug of choice for aspergillus prophylaxis in lung transplant recipients. Adverse effects unique to voriconazole include transient visual changes and hallucinations, both possibly linked to elevated drug concentrations. Itraconazole may be used in place of voriconazole if susceptibility permits. However, itraconazole administration is limited by poor bioavailability due to its lipophilicity. Itraconazole absorption is also dependent upon formulation: capsules require food or an acidic environment to increase absorption, and thus cannot be taken with antacids, histamine-2 receptor blockers, or proton pump inhibitors. On the other hand, itraconazole suspension provides 30% greater absorption and should be taken on an empty stomach.

Fluconazole is commonly utilized for targeted prophylaxis against dimorphic fungi, such as blastomycoses, histoplasma, or coccidioides, in heart transplant recipients. Drug-drug interactions are of significant concern with azole antifungals. Fluconazole is a potent inhibitor of CYP2C9 and potentiates the effects of warfarin to a much greater degree than itraconazole or voriconazole. Voriconazole and itraconazole, on the other hand, inhibit CYP3A4 more than fluconazole.

Therapeutic drug monitoring (TDM) for azole antifungals themselves (voriconazole, itraconazole) is increasingly being utilized to ensure adequate drug exposure. It is recommended to begin TDM once drug concentrations are at steady state, approximately two weeks after drug initiation.

Disclosure Statement:
The author has no conflicts of interest to disclose.

References:

The proliferation signal inhibitors (PSIs) or mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are two of the most recent immunosuppressants introduced for use in lung transplantation. The mechanism of action of PSIs is distinct from calcineurin inhibitors (CNIs), and complementary when utilized together. PSIs bind to the cytoplasmic protein FKBP-12, inhibiting a protein kinase, the mammalian target of rapamycin (mTOR). The mTOR is a key regulatory pathway for several biologic processes. Inhibition of mTOR results in blockade of T and B cell proliferation in response to cytokine signals.

Sirolimus was the first PSI available for use, while everolimus was later introduced with improved bioavailability and a distinct pharmacokinetic profile. The half-life of everolimus is 28 hours, considerably shorter than sirolimus (62 hours), which allows for steady state to be achieved more rapidly (4 vs. 6 days). PSIs are oxidized by the hepatic CYP3A isoenzyme and are substrates of P-glycoprotein (p-gp), an intestinal efflux pump. Thus, significant drug interactions result with inhibitors or inducers of CYP3A and p-gp, such asazole antifungals. Similar to CNIs, PSIs display a narrow therapeutic index. Target concentrations are dependent on many factors including time since transplant, number and severity of rejection and infection episodes, and concomitant immunosuppressants. When combined with CNIs, a trough should be targeted in the lower range of the therapeutic window. In the absence of a CNI, trough levels up to 12 ng/mL have been evaluated; however, higher troughs are associated with increased adverse effects with little incremental gain in efficacy.

Major adverse effects that have limited the use of PSIs after lung transplantation include impaired wound healing, particularly of the bronchial anastomosis, and pneumonitis. PSIs are known to cause delayed wound healing as a result of their antiproliferative effects, and sirolimus has been associated with cases of bronchial anastomotic dehiscence. Historically, PSIs have not routinely been introduced before the third post-operative month unless the endobronchial anastomoses have healed. Sirolimus, and, less commonly, everolimus, have been associated with a non-infective pneumonitis in lung transplant recipients. This is characterized by bilateral alveolo-interstitial lung infiltrates. Treatment consists of drug discontinuation, and symptom resolution typically occurs within three months.

Although PSIs do not directly affect glomerular filtration, they may cause histologic changes consistent with tubular toxicity. In acute renal failure, PSIs can inhibit full recovery of renal function by slowing glomerular healing. PSIs can also cause or worsen proteinuria; this effect may be explained by loss of the antiproteinuric effect of CNIs, interference with albumin reabsorption, or inhibitory effects on vascular endothelial growth factor. Other commonly reported side effects include dose-dependent reversible dyslipidemia (38-57%) and myelosuppression. Increasing data have supported the use of PSIs in kidney and heart transplantation, but there remains a lack of strong clinical data in lung transplantation. Early reports suggested that the antiproliferative effects of PSIs might be protective against the development of BOS; however, this has not been borne out by definitive studies comparing rates of BOS in patients receiving everolimus compared to azathioprine (AZA) or mycophenolate mofetil (MMF). Today, PSIs are utilized in lung transplantation in patients with renal impairment attributed to CNIs or when other immunosuppressants are ineffective or contraindicated. Neurotoxicity attributed to CNIs is problematic, the manifestations of which range from simple tremors or headaches to encephalopathy and seizures. The PSIs are an alternative option when adverse effects persist despite CNI substitution or dose modification. Both PSIs cross the blood brain barrier; however, neurotoxicity has not yet been reported with their use.

The incidence of cytomegalovirus (CMV) infection is significantly less in patients treated with PSIs as compared to MMF or AZA.
Given the detrimental effects of CMV infection on morbidity and long term outcomes in lung transplantation, this is a distinct advantage for PSIs.

The role of PSIs in lung transplantation has yet to be specifically defined. Compared to CNIs, the PSIs offer therapeutic advantages that can be useful in some recipients – relatively less nephrotoxicity, neurotoxicity, and a lower predilection to CMV infection. Their use, however, has not demonstrated improved survival and further evaluation is required to define their role in therapy.31

Disclosure Statement:
The authors have no conflicts of interest to disclose.

References:

“Proliferation Signal Inhibitors...” Continued


THERAPEUTIC DRUG MONITORING: A CRASH COURSE IN PHARMACOKINETICS
Spencer T Martin, PharmD, BCPS
New York-Presbyterian Hospital, New York, NY

The requirement for therapeutic drug monitoring (TDM) in cardiothoracic transplant recipients is virtually universal. According to the 2011 ISHLT Registry for adult heart and lung transplant recipients, over 90% of all patients are maintained on calcineurin inhibitor (CNI) therapy at one-year post-transplant.\(^1\)\(^2\) Despite the immunosuppressive protocol pursued, the need for accurate and appropriate TDM is essential considering the pursuit of balancing efficacy with potentially toxic side effects. In many cases TDM occurs on a daily basis in the inpatient setting and remains a constant focus of an individual’s care throughout the remainder of their lives regardless of their current state of health. Considering the regularity in which immunosuppressive therapies are monitored, we as practitioners often do so without fully understanding the pharmacokinetic theories upon which they’re based.

The pharmacokinetic measurement most closely related to efficacy is the area under the concentration curve (AUC). A patient’s AUC is a direct representation of total drug bioavailability and exposure during the time it takes for a drug to be excreted (\(t_{\infty}\)), and is calculated by dividing the amount of unchanged drug in circulation by the rate of clearance.\(^3\) A more simplified version of AUC known as abbreviated AUC, which only requires TDM during the first four hours after administration of a dose can be used to simplify the monitoring requirements (\(AUC_{0-4}\)). Factors directly impacting AUC include the total dose, route of administration and variability in absorption, distribution, metabolism and elimination. Although measurement of AUC is considered the gold standard for correlating TDM with efficacy, consistently coordinating such a strategy is complicated, time consuming, and difficult to coordinate.

Peak concentration (\(C_{\text{max}}\)) has been described as a reliable marker of efficacy and a more easily attainable measurement compared to AUC. Data suggesting that CNI drug levels observed two-hours post-administration (\(C_2\)) have a strong relationship with \(AUC_{0-4}\) are robust.\(^4\) This specific model for TDM can be consistently attained if multiple aspects of patient care are coordinated including timely drug delivery, medication administration, and blood draws two hours post-administration. The feasibility of monitoring \(C_2\) becomes more
uncertain in regards the outpatient arena, requiring that the patient play a larger roll in ensuring that drug levels are drawn precisely two hours after they self-administer a dose. Considering that all patients are generally instructed to take their CNI therapies at a predetermined time (e.g., 09:00, 21:00), this method may be more burdensome to accurately pursue as patient load increases.

The most frequently implemented TDM strategy in transplant recipients is the trending of trough levels (\(C_0\)), defined as the lowest concentration of medication a patient is exposed to, immediately prior to the next dose. All too often, we as practitioners accept and pursue \(C_0\) “goals” without fully understanding that they are based on a poor correlation to AUC. Monitoring \(C_0\) offers a simple and consistent marker for guiding therapy, but is the most unreliable marker of total medication exposure and efficacy. Due to the lack of coordination involved in ensuring an accurate level, this method is often utilized.

Regardless of the TDM plan chosen for the patient, major limitations exist in ensuring accuracy, and are often overlooked. Practitioners are forced to assume that patients are taking medications at the prescribed dose at the prescribed times, and that the levels are drawn exactly 12 hours after the previous dose if monitoring \(C_0\). Drug levels can be influenced by multiple factors including deviation in diet or eating habits, taking additional over-the-counter or prescription medications without practitioner awareness, self-prescribing with herbal remedies and teas, or converting between brand name to generic formulations without prescriber knowledge. Monitoring levels without recognition of external influences may result in unnecessary reductions or increases in dose, potentially producing an ineffective or toxic drug regimen.

A sound understanding of the pharmacokinetics related to the most frequently used medications are required to ensure optimal monitoring. Several strategies for TDM of CNIs have been validated, each displaying benefits and pitfalls. Despite an individual program’s preference for TDM strategy, constant evaluation of the accuracy and appropriateness of levels is a necessity. It is the responsibility of all members of the multidisciplinary team to remain vigilant in ensuring appropriate TDM to maintain the highest level of pharmaceutical and patient care.

Disclosure Statement: Dr. Martin produces continuing education for The Immunology Report, a group funded by an educational grant from Astellas Pharma US, Inc.

References:

EDITORS' RECOMMENDED ...

READING

from Luciano Potena:

*The Checklist Manifesto* by Atul Gawande

Says Luciano: “It is a very interesting essay from a surgeon working at Brigham’s Hospital in Boston, about the development of a checklists-based method to help doctors (and others) in doing a better job in complex tasking. Said in this way it seems boring, but it isn’t—it is easy reading and I passed through it in 5 days during the Christmas holidays.”

from Stan Martin:

*Reamde* by Neal Stephenson

Says Stan: “No, Reamde not a typo. It’s almost 1000 pages and I think my wife is going to divorce me because I can’t put it down at night. I can’t even begin to describe the imaginative genius and characterizations in this book. What a story!”

from Bronwyn Levey:

*The Help* by Kathryn Stockett

*The Mists of Avalon* by Marion Zimmer Bradley

Says Bronwyn: “It is essentially the magical saga of the women behind King Arthur’s throne, and what I love about it is that it looks at the history/legend of ‘King Arthur and his knights of the round table’ from a female perspective ... very interesting indeed!!

LISTENING

from Vincent Valentine:

The soundtrack from *Risky Business* (1983 movie written & directed by Paul Brickman):

- Old Time Rock & Roll (wma)
- The Dream Is Always The Same (wma)
- In the Air Tonight (wma)
- Every Breath You Take (mp3)
- Mannish Boy (wma)
- Swamp (wma)
- The Pump (wma)
- Two Hearts Beat As One (mp3) – not from the soundtrack, but thrown in for good measure

Vincent says: “This soundtrack has so many heart and lung references. It all ties in with the “risky business” of infections and drug therapies in heart and lung transplantation. While you’re at it, you might as well watch *Risky Business* again for old times sake and, this time, pay special attention to the young Tom Cruise, Bronson Pinchot, Curtis Armstrong, and Joe Pantoliano. We all know this movie made Tom Cruise an overnight mega star, but can you recall where you may have seen the rest? Do *Perfect Strangers*, *Revenge of the Nerds*, *Midnight Run*, or *The Fugitive* ring a bell?

VIEWING

from Vincent Valentine:

*Cujo* (1983), directed by Lewis Teague (novel by Stephen King)

A friendly St. Bernard named “Cujo” contracts rabies and conducts a reign of terror on a small American town.
“You can’t be a real country unless you have a beer and an airline - it helps if you have some kind of a football team, or some nuclear weapons, but at the very least you need a beer.”
- Frank Zappa

Historic Prague Bars

“A bar is better than a newspaper for public discussion.”
- Jim Parker, on the importance of a healthy pub culture

Prague Pubs

“24 hours in a day, 24 beers in a case. Coincidence?”
- Stephen Wright

Czech Traditional Pubs

“Make sure that the beer - four pints a week - goes to the troops under fire before any of the parties in the rear get a drop.” – Winston Churchill to his Secretary of War, 1944

Prague Beer Garden

“Without question, the greatest invention in the history of mankind is beer. Oh, I grant you that the wheel was also a fine invention, but the wheel does not go nearly as well with pizza.”
- Dave Barry