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New Perspectives on Microbial Organisms and Ophthalmic Infections Using ACSIKS Data

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Donald T.H. Tan, FRCS

At the 34th Congress of the Asia-Pacific Academy of Ophthalmology in Bangkok, Thailand, **Prashant Garg, MD**, LV Prasad Eye Institute, Hyderabad, India, and **Donald T.H. Tan, FRCS**, Singapore National Eye Centre, Singapore, provided their perspectives on the Asia Cornea Society Infectious Keratitis Study (ACSIKS) study, organisms that cause ophthalmic infections, and how the data may have an impact on antibiotic choices in both India and the Asia-Pacific region.

Corneal infections are one of the most prevalent causes of corneal opacity and loss of vision in many developing countries. The burden is much higher in the Asia-Pacific region. There are several reasons for this: the first is that a large population resides in the Asia-Pacific region. The second is related to socioeconomics, with many countries in the Asia-Pacific region having large numbers of residents from a lower or middle economic background, with agriculture or manual labor the predominant occupation. In these nations, corneal foreign body or abrasion is the most important risk factor for corneal infections. In contrast to developed countries, and especially in more urbanized populations, contact lens wear becomes a much more prominent risk factor for corneal infections.

In 2013, the Asia Cornea Society launched a multinational study in 8 countries and 27 sites to determine the risk factors for corneal infection, the epidemiology of causative organisms, antimicrobial susceptibility profiles, and treatment outcomes, with the overarching objective of finding ways to reduce the burden of blindness from this disease. The study sites were asked to enroll every case of keratitis using a preapproved study protocol. The cases were investigated using standardized microbiology protocols including comprehensive antibiotic susceptibility testing. The study duration was set at over a year and a half, with a target of enrolling 3,000 to 4,000 cases. The study ultimately had more than 6,500 cases of keratitis.

The above clinical study was considered Phase One of ACSIKS. In Phase Two, which is currently nearing completion, all cultured bacterial and fungal organisms have been subcultured and stored in central ACSIKS repositories in Singapore and India. Reidentification and categorization as well as more comprehensive susceptibility testing will be performed.

In the meantime, other countries, such as Indonesia and Vietnam, also have approached the Asia Cornea Society requesting to participate in ACSIKS. Dr. Tan believes there would be great benefit to have a secondary study including additional population samples. "The beauty of ACSIKS is that we can compare data among countries because the methodology is the same," he said. Finally, with the revalidated bacterial and fungal isolates in our central repository, additional focused microbiological sub-studies can be performed as part of Phase Three of ACSIKS, and these may include genotyping and mutational analysis of resistant organisms collected. This step will help clinicians understand how and why the organisms are developing resistance. In industry, the development of new antifungals and antibiotics can be enhanced by studying the collected samples that actually have caused community infection.

ACSIKS reveals antibiotic resistance patterns

From the ACSIKS data, there appeared to be a difference in types of organisms and antibiotic resistance patterns among the countries studied. For the type of organism, developing countries like India, China, and the Philippines, to some degree, saw more fungal organisms in contrast to bacteria as the dominant organism for developed countries (e.g., Singapore and Japan). Warmer climate countries and populations with a greater number of contact lens wearers (such as Singapore and Taiwan) showed more gram-negative organisms than gram-positive organisms. On the other hand, data from Japan revealed more gram-positive organisms present in culture samples. In Singapore, Thailand, and the Philippines, Pseudomonas aeruginosa was the primary organism found. Overall, there were more gram-positive organisms than gram-negative ones. There also was significant variability in antibiotic resistance among different countries. More industrialized countries, including Taiwan, Singapore, Korea, and Japan were found to have the lowest resistance to P. aeruginosa, with highest resistance in India, China, and the Philippines. Twenty one of 24 Pseudomonas isolates from India were resistant to multiple classes of antibiotics. Finally, the ACSIKS data revealed patterns in fluoroquinolone resistance. "The most resistant antibiotic to Pseudomonas aeruginosa was moxifloxacin, which is unfortunate because we use a lot of it in clinical practice," Dr. Tan said.

In India: Public health interventions are crucial

"The findings from ACSIKS give us some important tools as far as strategies that need to be adopted in order to prevent blindness from corneal infections," Dr. Garg said. The strategy Dr. Garg provided was to focus on public health education, especially in patients who are injured during farming or agriculture-related activities. He said that it is crucial for the community to be educated on not using homemade remedies, which is the current practice in rural areas of India and other developing nations, and instead to seek proper medical treatment. If patients experience corneal ulcers progressing in size or if a physician has little or no experience treating these types of patients, they should be referred to advanced tertiary care centers. Within these tertiary care centers, two strategies should be adopted, Dr. Garg said. One is to constantly monitor antibiotic susceptibility of the isolates from these patients, which will act as a guide for future patients presenting with corneal infections. Second, since the ACSIKS data showed that P. aeruginosa was resistant to multiple classes of antibiotics and that even fourth-generation fluoroquinolones are less effective against gram-positive organisms, these patients should be treated with combination therapy of cefazolin plus an aminoglycoside or a first-generation fluoroquinolone rather than monotherapy. Using combination therapy is helpful because the chances of developing drug resistance goes down.

Specifically for India, drug resistance has shifted to originate not only from hospitals but also from the community. According to Dr. Garg, this is due to the widespread use of antibiotics in poultry and cattle feed. With proper government intervention, community-acquired antibiotic resistance can slowly be overcome. Dr. Garg outlines four strategies. First, the Indian government should place strict regulations on prescribing antibiotics. Although most physicians want to treat their patients with the most potent and recent antibiotics, the use should be restricted to the most serious cases rather than common infections. Second, the use of antibiotics in poultry and agriculture needs to be regulated. Third, physicians must adopt strategies to prevent the spread of these drug-resistant organisms, such as proper hand hygiene. Finally, there needs to be a constant surveillance and reporting of the resistance trends in antibiotic susceptibility.

Furthermore, Dr. Garg is aware that the government is considering dispensing antibiotics as prescription only, but because the health infrastructure in India is poor, the government has not taken aggressive action. It is crucial to constantly monitor prescription patterns of antibiotics in hospitals, periodically check antibiotic policies, and check how physicians comply to the antibiotic policies created.

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Additionally, there also is a need for budget allocation for antibiotic resistance research. Dr. Garg has been working on a collaborative project with the aim of using polymeric formulations to improve drug retention and penetration into the corneal tissue. "We have polymeric material where the terminal ends are functionalized, and these polymeric material bind bacteria and fungi. The binding is specific, and we are trying to tag nanoparticles to these hyperbranched polymeric material so that when they enter the cornea, they will bind to the bacteria releasing the nanoformulation, thereby working as a target for drug delivery," he said. With increased funds for research, the development of both new and existing drugs can increase efficacy in treating infections.

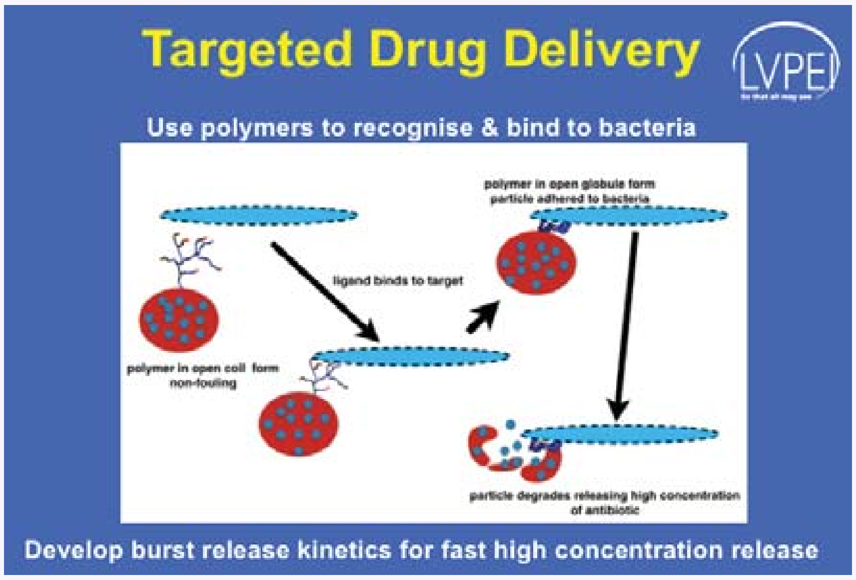

Figure 1: Use of bacteria binding polymers for drug delivery

Source: Prashant Garg, MD

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Developed countries can still take preventable measures

In Singapore and other developed countries, Dr. Tan emphasizes that prevention measures should focus on proper contact lens wear and appropriate regulatory oversight in the purchasing and prescribing of contact lenses. In these countries, there are problems with buying contact lenses through the internet and with young teenagers sharing colored contact lenses. By having proper contact lens hygiene as well as qualified optometrists and contact lens practitioners who fit lenses appropriately, infection rates can decrease. Another related public health measure that can help to prevent infection is work-related trauma. In industrial work environments and the farming industry, a chemical injury in the factory or an agricultural abrasion may lead to fungal infection. In these cases, the use of safety glasses and appropriate eye protection is important.

The use of newer fluoroquinolones in keratitis

Fluoroquinolones have become an integral part of treating corneal infections. As the newer class of fourth-generation fluoroquinolones have been enhanced, they have a slightly broader spectrum of coverage. As mentioned earlier, moxifloxacin showed the greatest resistance in the ACSIKS data. For Dr. Tan in Singapore, he is moving away from moxifloxacin

Antibiotic Resistance

8-methoxy fluoroquinolone

LVPEI

	Ciprofloxacin	Gatifloxacin	Moxifloxacin
Cipro sensitive *Gram* + ive	0.3 (0.08-1)	0.09 (0.03-0.5)	0.09 (0.03-0.5)
Cipro resistant Gram + ive	32 (4-32)	1.5 (0-32)	1.75 (0.2-32)
Cipro sensitive *Gram* - ive	0.19 (0.13-0.75)	0.5 (0.05-3)	2 (0.13-8)
Cipro resistant *Gram* - ive	32 (32-32)	32 (32-32)	32 (32-32)

MIC 90 in 2002

Figure 2A: Comparison of MIC values of first and fourth generation quinolones against clinical isolates in 2002. The values clearly show that the fourth generation quinolones had an excellent activity against ciprofloxacin resistant gram positive isolates.

Source: Prashant Garg, MD

Antibiotic Resistance

8-methoxy fluoroquinolone

LVPEI

Organism	Susceptibility		
	N	Gatifloxacin sensitivity (%)	Moxifloxacin sensitivity (%)
Cipro sensitive *S.aureus*	39	100	94.9
Cipro resistant *S.aureus*	97	41.2	7.2
Cipro sensitive *CONS*	120	100	85.3
Cipro resistant CONS	111	75.7	25.2
Cipro sensitive *S.pneumoniae*	301	97.7	83.5
Cipro resistant *S.pneumoniae*	5	40	20

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Figure 2B: Activity of fourth generation quinolones against ciprofloxacin resistant isolates as determined in 2009. The figures clearly show marked reduction in susceptibility against ciprofloxacin resistant isolates, compared to 2002 data, when these molecules were introduced.

Source: Prashant Garg, MD

and more towards levofloxacin. In recent years, Singapore has had access to high-concentration 1.5% levofloxacin in a preservative-free commercial preparation. With severe cases of keratitis, an hourly 1.5% levofloxacin solution combined with a cephalosporin can cover a broad range of gram-positive and gram-negative organisms at a high concentration. Levofloxacin has a high safety profile with minimal toxicity. This safety profile is one reason levofloxacin is available commercially in a high concentration and why other antibiotics may not be available at such a high concentration. For countries without the commercially available 1.5% levofloxacin, Dr. Tan says the use of a fortified antibiotic is useful. The fortified antibiotic consists of compounding a higher concentration of an aminoglycoside or cefazolin, which can then be used aggressively every hour to try to increase the concentration of the drug once administered to rapidly kill the bacteria.

As for Dr. Garg's perspective on the use of fluoroquinolones, he believes that the newer class of fluoroquinolones should include four drugs: levofloxacin, besifloxacin, gatifloxacin, and moxifloxacin, with the latter two used in clinical practice for a sufficient length of time. Analyzing the data on those two drugs' susceptibility, Dr. Garg sees an increasing level of resistance among gram-positive organisms, especially the ciprofloxacin-resistant gram-positive organisms. However, these data may not translate directly to levofloxacin and besifloxacin because these molecules are not on the market in some areas and may not be commonly used in practice. Because of these two factors, Dr. Garg expects that these drugs will have much better activity than gatifloxacin and moxifloxacin. In his own research, Dr. Garg found that enhancing corneal penetration can be accomplished by modifying the formulation of these agents. Further, increasing the concentrations of levofloxacin and besifloxacin is likely to increase corneal concentration, resulting in more effective eradication of organisms.

In Dr. Garg's practice, he realized in 2005 that many organisms started to show resistance. He then switched from using first-generation fluoroquinolones to fourth-generation fluoroquinolones in less severe cases. In more severe keratitis cases, a combination of cefazolin plus an aminoglycoside was used. Since then, Dr. Garg has moved to treating all bacterial infections with a combination drug therapy of cefazolin plus an aminoglycoside or ciprofloxacin. The limiting factor for Dr. Garg is that cefazolin is not available as an ophthalmic preparation and aminoglycosides are lower in concentration, so both drugs must be formulated before dispensing to the patient. "We are trying to work with the industry in order to identify ways to overcome the non-availability of these antibiotics," Dr. Garg said.