A **CONTINUING MEDICAL EDUCATION** PUBLICATION

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TOPICS IN Ocular Antiinfectives

Flap-related Infections

Steven Schallhorn, MD

Corneal infection after creation of a lamellar flap is a potentially devastating complication of LASIK. As demonstrated by the steadily falling number of infectious keratitis cases following corneal refractive surgery, the risk of infection can be reduced through surgical technique, increased awareness, and proper prophylaxis.

Laser in situ keratomileusis (LASIK) is the most commonly performed refractive surgery in the world today. One rare but potentially sight-threatening complication after LASIK is infectious keratitis. Due to epithelial preservation, LASIK is presumably associated with a reduced risk of infection compared with surface ablation procedures.[1] Still, when the interface does become infected, serious sequelae such as flap melting, severe irregular astigmatism, and corneal scarring may ensue and can reduce vision. Considering that patients who choose to undergo LASIK usually have excellent corrected vision, minimizing the risk of postoperative infection is of great importance to ensure the best outcome.

What's more, the risk of interface infection is no longer restricted to LASIK—some newer and increasingly performed refractive procedures, such as corneal inlay insertion and refractive lenticular extraction, involve a lamellar dissection that may introduce organisms into the stroma, even without creation of a flap.

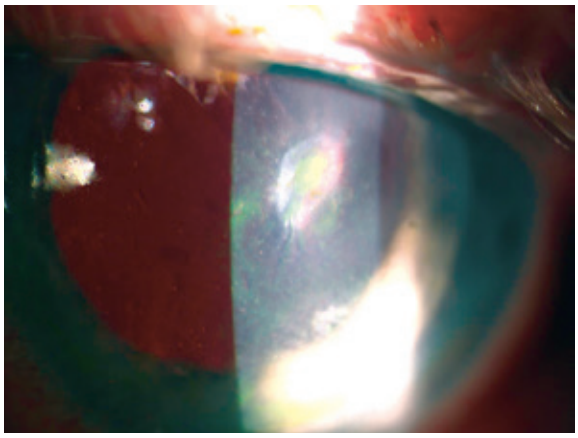

FIGURE 1 Photograph of infectious keratitis in a 43-year-old female following uneventful LASIK using a mechanical keratome, 14 days postop. Note the focal area of infiltration with surrounding inflammation. *(Courtesy Steven Schallhorn, MD.)*

The Changing Trends

The incidence of infectious keratitis after LASIK can vary widely (0% to 1.5%) depending on the population studied.[2] But there appears to be a general trend toward fewer infections over the past decade and a half. According to a survey conducted by the American Society of Cataract and Refractive Surgery (ASCRS) in the year 2001, the incidence of post-LASIK infectious keratitis at the time was 1 infection in every 2919 procedures.[3] A second ASCRS survey, conducted in 2004, showed that the infection rate following photorefractive keratectomy (PRK) and LASIK was 1 in every

See INSIDE for:

Factors in Infectious Complications of Corneal Transplant

by Bennie H. Jeng, MD

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Explain changing trends in infectious keratitis following LASIK.
2. Minimize the risk of flap-related infections in LASIK patients by improving surgical and clinical approaches.
3. Describe factors related to the increase in fungal infection incidence following corneal transplantation.
4. Reduce risk for bacterial and fungal infection in corneal transplant recipients.

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2131 procedures.[1] The organization surveyed its members yet again in 2008 and reported an incidence of 1 corneal infection in every 1102 keratorefractive procedures.[4]

In two large retrospective case series, investigators in Spain observed a similar decreasing trend in the incidence of post-LASIK infectious keratitis, which fell from 0.035% (about 1 in 2857) between 2002 and 2008, to 0.011% (about 1 in 9091) between 2010 and 2013.[5,6] In addition, their data corroborates that corneal infections occur less frequently after LASIK than after surface ablation procedures. The incidence rate of infectious keratitis after surface ablation during the same two time periods was 0.200% and 0.066%, respectively, about 6 times higher than after LASIK.[5,6]

An analysis of procedures conducted at Optical Express from 2009 to 2010 had similar findings. Of the 185,019 eyes of 95,123 patients that underwent laser vision correction, the incidence of microbial keratitis was higher after PRK than LASIK (1:3,100 vs 1:6,700, respectively) and for LASIK cases that underwent a mechanical keratome compared to a femtosecond laser created flap (1:4,000 vs 1:7,7000, respectively).[7]

Surgical Developments

There is little doubt that increased caution and awareness has contributed to the decrease in the overall incidence of post-refractive-surgery infection. The refinement of surgical techniques may have played a role too. One major technological advance in LASIK over the past decade is the use of a femtosecond laser to create the lamellar corneal flap. Unlike a microkeratome blade, the femtosecond laser creates a flap by delivering laser pulses at a predetermined depth in the cornea. Without the introduction of surgical instruments within the intrastromal area, it is in essence a sterile technique.

For the conventional mechanical microkeratome method, it is notable that instrument sterilization techniques have been improved, albeit driven largely

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STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread "off-label" use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.[1]
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.[2]
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.[3]
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.[4]
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).[5,6]
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

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by an effort to reduce the incidence of diffuse lamellar keratitis (DLK). A noninfectious condition of the lamellar interface following LASIK, DLK is thought to be an inflammatory response triggered by miscellaneous stimuli on the stromal bed.[8] As shown in several studies, alterations to instrument cleaning procedures can be made to significantly reduce the occurrence of DLK.[9,10] This has increased awareness of proper sterilization techniques for lamellar procedures, which have likely had an impact on infection rates.

Prophylactic Measures

Perhaps most of all, the decrease in the number of infections can be attributed to prophylactic use of broad-spectrum antibiotic drops. Now the antibiotic class most commonly prescribed following corneal laser refractive surgery for infection prevention is the newer fluoroquinolones. The addition of moxifloxacin—a fourth-generation fluoroquinolone that became available in Spain in 2010—to routine antibiotic prophylaxis is believed to be responsible for the dramatic reduction in the frequency of infection after LASIK found in the study from Spain.[6] The prophylactic antibiotic drops are usually dosed four times daily, starting on the day of surgery and continuing postoperatively for four to seven days. Some surgeons give antibiotics before the day of surgery too, with the aim of further reducing the risk of infection.

Prophylactic antibiotic drops are not without downsides. They add to surgery costs and can sometimes cause epithelial toxicity and breakdown leading to secondary infection. In addition, topically applied ophthalmic antibiotics have the potential to alter the profile and resistance pattern of bacterial isolates from the ocular surface.[11,12]

One important patient factor to consider in minimizing the risk for infection is preexisting infectious eyelid disease such as blepharitis. Theoretically, decreasing the bacterial load on the ocular surface could reduce the risk for bacterial keratitis. All patients considering refractive surgery should therefore undergo a thorough examination of the eyelids and lacrimal apparatus. Some surgeons recommend additional prophylactic steps for the prevention of infection, including lid preparation with povidone iodine, use of sterile drapes, gowns, gloves, and masks, and performing monocular surgery or using a separate set of instruments when performing bilateral surgery.[4]

Changing Pathogens

The predominant organisms in infectious keratitis following LASIK at present are different from those encountered by refractive surgeons 15 years ago. In the first ASCRS survey, the most common organisms cultured were atypical mycobacteria (28%) and staphylococci (20%) species.[3] A systemic review of the published literature prior to the year 2003 identified more than 100 infections following LASIK, with 47% caused by atypical mycobacteria and 19% by staphylococcal species.[13] The first few years of the last decade also saw clusters or outbreaks of mycobacterial infections following LASIK.[14-17] At least some of these were associated with the use of nonsterile water to clean instruments or use of ice during surgery.[17] To reduce the risk of infection, especially mycobacterial infection, only sterile fluids should be applied to the eye before, during, and after LASIK.[1]

The preponderance of mycobacteria-related opportunistic infections, as it turned out, was short-lived. In the 2004 and 2008 ASCRS surveys, cases of atypical mycobacteria had dropped to 5% and zero, respectively.[4] No patient who received prophylaxis with a fourth-generation fluoroquinolone experienced an infection with atypical mycobacteria. Meantime, gram-positive bacteria—particularly Staphylococci—became more common. In 2008, the most frequently cultured organism (28%) was methicillin-resistant *Staphylococcus aureus* (MRSA).[4] Interestingly, this shift in the pattern of causative microorganism corresponds with the increased use of newer fluoroquinolones. This may not be a coincidence: the fourth-generation fluoroquinolones have improved potency against mycobacteria but are less effective for resistant infections caused by MRSA.[18,19]

CORE CONCEPTS

- Infectious keratitis is a serious flap-related complication after LASIK. Postoperative corneal infections occur less frequently after LASIK than after surface ablation procedures, presumably because flap creation allows preservation of epithelium integrity.
- With increased use of newer fluoroquinolones, the incidence of infectious keratitis following keratorefractive procedures has significantly decreased. Additional factors that may have contributed to the decreasing rate of infection include increased caution, increased use of femtosecond laser, and improved sterile techniques.
- Over the last 15 years, there has been a marked change in the microbes responsible for infections after flap creation in LASIK. While opportunistic infections related to atypical mycobacteria fell to zero, gram-positive bacteria, particularly MRSA, rose as the main cause of post-LASIK infection.
- Appropriate management of infectious keratitis following LASIK requires a high degree of suspicion combined with rapid recognition. The recommended approaches for the treatment of post-LASIK infectious keratitis include culture of the flap interface and empiric therapy with aggressive broad-spectrum antibiotic agents.

Managing Flap-related Infections

What is most important for the management of post-LASIK infection is recognition. The primary signs of infection—redness, pain, and blurred vision—are not specific; there are other postoperative complications that often resemble infection in appearance: DLK,

central toxic keratopathy (CTK), or pressure-induced steroid keratopathy (PISK). Certain signs could help differentiate infection from other noninfectious conditions. DLK, for example, has a characteristic diffuse appearance, whereas infectious keratitis typically has a focal infiltrate surrounded by inflammation, sometimes with satellite infiltrates depending on the causative organism (Figure 1).[1] Even so, recognizing infection within the flap interface can be difficult. For rapid diagnosis and timely treatment, maintaining a high degree of suspicion is the key.

The treatment routine for infectious keratitis is fairly straightforward once the presumptive diagnosis is established: culture of the flap interface followed by intensive broad-spectrum antibiotics. The treatment process, of course, should be individualized. If a patient comes in with a necrotic flap from an infection, it may be best to simply amputate the flap. Flap amputation may limit the infectious process and allow better penetration of antibiotics; the lamellar flap can be sent for culture to determine the cause of infection. In cases where the appearance of the infiltrate points to a particular type of pathogen (a feathery-edged infiltrate with satellite lesions, for example, is a characteristic feature of fungal infection), empiric antibiotic therapy should be reassessed and tailored.

Conclusions

Incidence rates of infectious keratitis after LASIK have been falling during the past decade and a half, likely a result of multiple factors including changed prophylactic antibiotics, improved sterile techniques, and greater awareness. Effective prevention of post-LASIK infection requires due diligence prior to, during, and following the procedure.

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Factors in Infectious Complications of Corneal Transplant

Bennie H. Jeng, MD

Post-keratoplasty fungal infections are on the rise. With lamellar keratoplasty now more commonly performed than penetrating keratoplasty, is it time to get serious about preventing fungal infection in corneal transplant recipients?

About 45,000 corneal transplants are performed in the US each year for various indications including Fuchs' endothelial dystrophy (22%), pseudophakic bullous keratopathy (PBK) (12%), keratoconus (10%), and regrafting (10%).[1] (The incidence of cataract surgery-induced corneal edema has decreased in recent years due to improved surgical techniques; however, PBK still remains a leading indication for corneal transplantation.) For every 10,000 corneal transplants performed across indications, about 7 become compromised due to corneal infection or endophthalmitis. In 2014, for example, 18 cases of infectious keratitis and 15 cases of endophthalmitis resulted following roughly 46,500 total procedures.[2] The consequences of transplant infection—including scarring, graft failure, and in the case of endophthalmitis, the potential for loss of the eye—are often severe.

Infection Rates

While infection rates have remained consistently low in recent years, one trend has many within the ophthalmology community concerned: an increasing proportion of post-transplant fungal infections. *Candida* species were the most commonly identified pathogens among post-transplant keratitis and endophthalmitis cases in 2014, specifically *C. albicans* and *C. glabrata*.[2] A constellation of factors is likely involved in the increasing incidence of fungal infection following keratoplasty: among them are newer surgical methods, new tissue preparation techniques, and a storage medium that has not changed since the 1990s.

Lamellar Interface

The development of and increasing use of lamellar techniques (specifically Descemet-stripping endothelial keratoplasty [DSEK] and Descemet membrane endothelial keratoplasty [DMEK]) have lowered corneal transplant recipients' risk for rejection, reduced rates of astigmatism, and allowed for faster visual recovery compared with formerly popular full thickness methods. As a result, lamellar keratoplasty (LK), and specifically endothelial keratoplasty (EK), has overtaken penetrating keratoplasty (PK) in popularity. In 2005, only 5% of corneal transplantations performed used EK and 95% were PK; by 2014, 58% were EK and 42% were PK.[1]

It is easy to see how the rapid rise in use of lamellar techniques might contribute to post-keratoplasty fungal infection when one considers their anatomical differences. Unlike full-thickness grafting, EK involves floating a piece of donor tissue up against host tissue. This creates an interface where fungal contaminants can become trapped, replicate, and cause an infection over ensuing days to months.

Cornea Precutting

Another major trend in the past decade is surgeons' increased use of eye bank-prepared precut donor corneas for grafting rather than cutting the graft themselves in the operating room. Among EK procedures performed in 2014, 58% used precut corneas.[1] Using precut corneas is desirable because it reduces operating room time, minimizes tissue waste, and is associated with similar outcomes compared with surgeon-cut corneas.[3] Studies show that experienced, high-volume technicians have excellent thickness accuracy and quite low cut-failure rates.[3]

But there has been some suggestion that precut grafts may be associated with higher infection rates, possibly as the result of needing to warm them to room temperature for the cutting, then cycle back to 4° before shipping to the surgeon. A review of fungal infection cases occurring between 2007 and 2010 conducted by the Eye Bank Association of America (EBAA) medical advisory board revealed that 65% (11 of 17) of fungal infections were associated with precut tissue, whereas 35% (6 of 17) were surgeon cut, although the difference was not statistically significant.[4] According to a recent laboratory study by Tu and colleagues, the warming step in the eye bank protocol is capable of amplifying fungal replication 100-fold.[5] This step, followed by re-immersion in media (that does not contain an antifungal agent—see below) may set the stage for fungal infection in the recipient.

CORE CONCEPTS

- Fungal infections following corneal transplantation are uncommon but have increased in rate.
- Current US corneal storage media do not contain antifungal agent.
- Many factors are potentially involved in the increasing rate of fungal infections post-keratoplasty.
- Corneal rim cultures at time of surgery can guide therapy if positive for fungus.
- Addition of antifungals to corneal storage media may reduce fungal infection rates post-transplant.

Storage Media

As a matter of routine, eye banks employ rigorous standards to mitigate the risk of infection transmission and ensure quality tissue and processing, particularly as it pertains to viruses. Serologic tests rule out key transmittable viruses—including HIV, hepatitis B and C, HTLV, and West Nile Virus—as well as syphilis (a spirochete). Cause of death is also taken into account; patients who have a history of neurologic symptoms, such as delirium or dementia, are ineligible to be corneal donors due to concern for undiagnosed prion disease, eg, Creutzfeld-Jacob disease, which is not easily detectable by standard methods. Further, individuals whose death is related to sepsis or whose cause of death is unknown are also ineligible for corneal tissue donation.[6]

Antimicrobial activity of corneal graft storage media prevents contamination and reduces the risk for transmission of susceptible bacterial pathogens from donor to host. Many post-surgical bacterial and fungal infections are thought to be donor derived (rather than host derived or perisurgically acquired). Cadaveric corneal tissue deemed suitable for transplant may be stored for up to 14 days prior to release, typically in Optisol GS (Bausch & Lomb, Rochester, NY). The G and S in Optisol GS refer to gentamycin and streptomycin, which prevent bacterial contamination during storage and play a major role in preventing post-keratoplasty infection.[7] Since its introduction about 25 years ago, Optisol-preserved corneal transplants have been associated with an extremely low incidence of post-keratoplasty bacterial infection.

However, Optisol GS and other storage solutions available in the US contain no antifungal agent. The ophthalmology community is divided as to whether an antifungal additive to corneal storage solution is warranted. In the EBAA medical advisory board subcommittee noted above, which reviewed post-keratoplasty fungal infections reported between 2007 and 2010 in an attempt to address the potential benefit of antifungal addition to storage media, the authors concluded that antifungal supplementation to storage media was not recommended at present based on high cost-to-benefit ratio and insufficient data on the safety of voriconazole.[4]

However, it remains possible that a less expensive antifungal, such as amphotericin, might be a feasible alternative. Amphotericin has long been a component of corneal storage solutions used in Europe, where graft tissue is maintained for longer durations (up to 7 weeks) at higher temperatures according to typical organ culture media protocol.[8] Layer and associates recently investigated the antifungal activity of Optisol GS supplemented with either voriconazole or amphotericin and the safety of using antifungal-supplemented solutions as storage media for corneal donor tissue.[9] They found that all concentrations of amphotericin tested were superior to voriconazole for preventing *Candida* growth, and that solutions with lower concentrations of amphotericin were comparable to control solutions (without antifungal) in terms of endothelial cell count and tissue viability.

These findings are promising; however, further studies are needed to address safety, formulation stability, and other issues before antifungal supplementation of storage media can be recommended.

Corneal Rim Culture

In recent years, many corneal transplant surgeons have dropped corneal rim cultures from their protocols, arguing that they are not cost effective, rarely grow, and do not provide actionable information even when they do. A study showed that a positive bacterial corneal rim culture taken at the time of surgery does not predict infection and, among patients who do become infected, that species are not necessarily concordant.

Some concordance has been demonstrated, however, between fungal corneal rim cultures and later cultures of the recipient's eye. Although positive preoperative fungal cultures rarely grow, those that do have been associated with a 17% rate of transplant-related fungal keratitis or endophthalmitis; that's far greater than a baseline risk of 0.07%.[10] For these reasons, I think that obtaining routine corneal rim cultures at the time of surgery is still advisable, particularly in light of increasing fungal infection rates. What to do with a positive fungal corneal rim culture in a patient who is otherwise doing well is another point of contention. Some would go ahead and start antifungal therapy for that patient out of concern that a subclinical infection might be brewing; others would simply follow the patient more closely.

Routine Prevention

It is important that blepharitis, if present, be detected and corrected prior to surgery, since increased bacterial load on the lids can increase patient risk for post-operative infection. Betadine (povidone-iodine) prep remains the only measure that has been proven to reduce the incidence of post-operative infection in cataract surgery.[11] Extrapolating from that data, meticulous antiseptic preparation to the periorbital skin and ocular surface of sufficient time (leaving povidone-iodine in contact with the ocular surface for 5 to 15 minutes) is standard of care for all ocular surgeries, including corneal transplantation.

Post-operative topical antibacterials are routinely provided following surgery; a fluoroquinolone or polymyxin B-trimethoprim are popular choices for their broad coverage.

Conclusion

Post-transplant fungal infections are rare but potentially devastating. Additional studies on antifungal supplementation to corneal storage media could pave the way to lowering risk even further.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 60

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1–10) and in the Evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. There is no fee to participate in this activity. *You can take the test online at* **http://cme.ufl.edu/ocular**.

1. Which of following statements is true about microbial keratitis trends following refractive surgery over the past 15 years?
   A. The overall rate of infection has markedly decreased
   B. The overall rate of infection has markedly increased
   C. The rate of infection after flap creation is higher than after surface ablation
   D. Opportunistic infections have become much more common

2. Which of the following is NOT a part of routine screening performed on donor corneas?
   A. Varicella Zoster Virus
   B. *Acanthamoeba*
   C. HIV
   D. A and B

3. Which of the following organisms is responsible for an increasing proportion of post-keratoplasty infections?
   A. *Candida* spp.
   B. *Micrococcus* spp.
   C. *Corynebacterium* spp.
   D. West Nile Virus

4. Which of the following findings is inconsistent with infectious keratitis following LASIK?
   A. A focal infiltrate
   B. Diffuse intralamellar inflammation
   C. Satellite infiltrates
   D. Decreased vision

5. European and US corneal grafting practices differ in which of the following ways?
   A. Temperature of storage
   B. Potential duration of storage
   C. Storage media contents
   D. All of the above

6. Which of the following organisms is the most common cause of infectious keratitis after LASIK according to the most recent ASCRS survey?
   A. Atypical mycobacteria
   B. Non-MRSA Staphylococci
   C. MRSA
   D. *Acanthamoeba*

7. According to 2014 EBAA data, which of the following is NOT a leading indication for corneal transplantation?
   A. Fuchs' endothelial dystrophy
   B. Lisch corneal dystrophy
   C. Pseudophakic bullous keratopathy
   D. Regrafting

8. Which of the following strategies may help reduce the risk of corneal infection after LASIK?
   A. Examination of the eyelids prior to surgery
   B. Use of sterile fluids during surgery
   C. Postoperative prophylaxis with moxifloxacin
   D. All of the above

9. Which of the following may play a role in increased rates of fungal infection following transplant?
   A. Use of precut grafts
   B. Lack of antifungal agent in storage medium
   C. Increased popularity of EK
   D. All of the above

10. Which of the following practices has been associated with the epidemics of mycobacterial infections following LASIK at the beginning of the last decade?
    A. Use of contact lenses after surgery
    B. Use of contaminated fluids during surgery
    C. Use of ice during surgery
    D. Both B and C

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 60

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires March 31, 2017.

ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified:
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
    Objective 3: 1 2 3 4 5
    Objective 4: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

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