Special-Ops Opht

With the continuing rise of resistant bacteria, once-reliable drugs are rapidly becoming obsolete.

Here are strategies and tactics for fighting back.

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ADAPTED FROM AN ILLUSTRATION BY BJÖRN NORBERG

halmology *in the Age of Antibiotic Resistance*

BY ANNIE STUART, CONTRIBUTING WRITER

"WE'RE SEEING MOTHER NATURE AT HER BEST," said John D. Sheppard, MD, clinical director of the Lee Center for Ocular Pharmacology at Eastern Virginia Medical School in Norfolk, Va. "Quintillions of organisms adapting en masse to environmental stress, which is antibiotics."

Among these organisms, staphylococci are, perhaps, the source of greatest concern. According to Dr. Sheppard, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) are increasingly common causes of infectious conjunctivitis, keratitis, endophthalmitis, and preseptal and orbital cellulitis. Both the community-acquired and the more virulent hospital-acquired strains of methicillin-resistant organisms are on the rise.

"Within the next decade, we may find that 100 percent of the staph we culture in ophthalmic practice is methicillin resistant," he said. "And that phenomenon may be eerily similar to what we saw in the 1960s, when virtually all staph became penicillin resistant, and in the '70s, when pneumococci grew increasingly resistant to a wide variety of antibiotics."

Have we learned anything from that earlier experience to avoid repeating history? The first step is to size up the enemy and determine exactly what kinds of challenges ophthalmologists are now facing—and, just as important, what ophthalmologists can contribute to the fight against growing resistance.

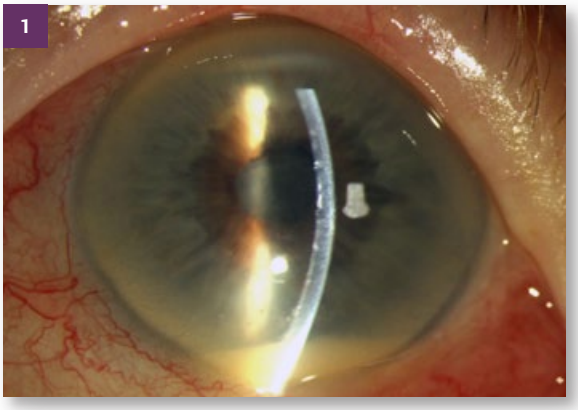
RESISTANCE—A MOVING TARGET

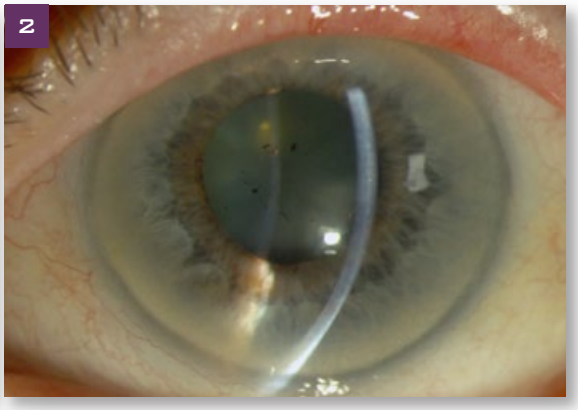
Once confined to hospitals, MRSA is advancing into the community and into ophthalmology clinics.

Not just a hospital problem. At 10 U.S. sites last year, cataract surgeons isolated methicillin-resistant staph from the eyelids and conjunctiva of about 40 percent of their patients, 90 percent of whom had no prior exposure to hospital environments,[1] demonstrating the growing prevalence of community-acquired resistance. And even though this type of resistance is generally less virulent than that acquired in hospital settings, said Dr. Sheppard, any resulting postoperative endophthalmitis is still devastating for patient and surgeon alike.

In the same study, higher levels of resistant staph were found in areas of the country with large poultry industries. This is likely not a coincidence, said lead author Randall J. Olson, MD, director of the Moran Eye Center at the University of Utah in Salt Lake City. Along with livestock industries, he said, poultry producers are one of the biggest offenders in the development of community-acquired resistance due to their continual use of newer and stronger antibiotics in animal feed.

"Until the poultry and livestock industry practices change," said Dr. Olson, "what we do is like spitting in the ocean. Physicians have a role to play, but it pales by comparison."





MRSE ENDOPHTHALMITIS. (1) Despite receiving prophylactic moxifloxacin topical drops immediately after an intravitreal injection, this 82-year-old patient presented four days later with pain, blurred vision and redness in the left eye. Her anterior chamber showed diffuse fibrin and a hypopyon, and VA was light perception. (2) One month later, after being treated with vitreous aspiration and intravitreal vancomycin, ceftazadime and dexamethasone, the infection was resolved, but VA was 20/400.

HARRY W. FLYNN JR., MD

Ophthalmologists must battle against bugs. Ophthalmologists account for only a sliver of overall antimicrobial use. But they still need to be careful; mass quantities of systemic antibiotics aren't required to prompt resistance, said David G. Hwang, MD, professor of ophthalmology and codirector of the cornea service and director of the refractive surgery service at the University of California, San Francisco. Suboptimal topical ophthalmic prescribing patterns can lead to increased development of local, yet clinically relevant, antibiotic-resistant infections. Prior topical ophthalmic fluoroquinolone use has been identified as a risk factor for subsequent development of fluoroquinolone-resistant ocular infections.[2]

Unfortunately, with increasing resistance, fewer options remain for treating these superbugs, said Dr. Olson. Moreover, overall production of antibiotics is reduced due to financial disincentives for pharmaceutical companies.

"There's a growing awareness that the solution is not just the next drug in the pipeline," said Dr. Hwang. This is true not only because the pipeline has meager offerings but also because simply reaching for the latest and greatest antimicrobial relentlessly leads to resistance—and more quickly than many might expect. Resistance has emerged against even the newest fluoroquinolones, which can't be relied upon to effectively treat MRSE and MRSA.[3]

Fluoroquinolones: part of the problem. Ocular TRUST (Tracking Resistance in U.S. Today), an annual report on in vitro antimicrobial susceptibility, shows consistent patterns of resistance against second- to fourth-generation fluoroquinolones, with about one-third of MRSE resistant to all four commonly prescribed fluoroquinolones, said Dr. Sheppard. "Alarmingly, more than 80 percent of MRSA were also resistant across the board at the same percentages," he said. "With increasing resistance, the strategy needs to be *prevention* of these infections."

Fluoroquinolones may be particularly likely to promote the development of antimicrobial resistance in real-world clinical usage, said Dr. Hwang. When dosed ideally, fluoroquinolones disrupt the fidelity of DNA replication, exerting a bactericidal effect. But when used inadequately, because of either inappropriate prescribing or patient noncompliance, their mechanism of action may actually rev up resistance because the surviving bacteria show a greatly increased random mutation rate.

"By not killing off the enemy and supplying them with small arms," Dr. Hwang said, "you allow them to overcome your defenses more easily." The longer you treat with a sublethal dose, the greater the cumulative acquisition of mutations, which confers a survival advantage. "The mutated organisms multiply rapidly from just a few to a large proportion of the bacterial flora, and this can happen in a matter of weeks," he said.

Tactic: target the mutants. A key principle, said Dr. Hwang, is to hit hard and get out fast. Ideally, you should aim for a target called the *mutant prevention concentration (MPC),* which for fluoroquinolones is typically three to four times higher than the minimum inhibitory concentration (MIC). At the MPC, the likelihood of development of mutational resistance in any given exposed bacterium is less than one in 10.[4]

When given early and in sufficient concentrations, the newer fluoroquinolones, including gatifloxacin, moxifloxacin and besifloxacin, are better than the older ones at achieving the MPC because of their increased potency (i.e., lower MICs)

against gram-positive cocci in particular. "So even if patients don't dose as frequently, peak antibiotic tissue levels can be well in excess of the MIC and can approach the MPC," Dr. Hwang said. Unfortunately, this benefit applies largely to methicillin-susceptible staphylococci, and even these newest fluoroquinolones cannot be relied upon to clear established MRSA infections.

ROUTES AND RATES OF INFECTION

Among common ophthalmic procedures, including intravitreal injections of anti-VEGF agents and refractive or cataract surgery, rates of infection remain relatively low. However, each type of procedure poses specific challenges.

Intravitreal injections. According to a large meta-analysis,[5] the most common organisms encountered with intravitreal injections are the coagulase-negative staphylococci and streptococci, said Harry W. Flynn Jr., MD, professor of ophthalmology at Bascom Palmer Eye Institute in Miami.

"*Staphylococcus* is the most common bacterial isolate cultured in postinjection endophthalmitis. *Streptococcus* is right behind, in second place, and occurs more frequently in injection-related than in post–cataract surgery endophthalmitis," he said. One theory is that aerosolized moisture droplets from talking, coughing, sneezing or breathing over the patient during injection may contaminate the needle or the field around the eye.[5]

Although the rate of infection with intravitreal injections is still low—between one in 2,000 and one in 5,000 injections, said Dr. Flynn, the number of injections has markedly increased in recent years. Certain practices may not readily show a difference on a per-injection basis, said Dr. Hwang, but the magnitude increases with multiple injections given over a multiyear treatment regimen and may make a clinically and statistically meaningful difference in the cumulative risk of endophthalmitis.

Refractive surgery. Because refractive procedures are generally performed in an office setting with high patient traffic, there is a potential for breaks in sterile processing or introduction of adventitious bacteria into the surgical field, said Dr. Hwang. Atypical mycobacteria, an important cause of post-LASIK infection, can be found in ultrasound water baths used for instrument processing or in tap water or moisture that gains entry into the surgical field, he said. "Fortunately, the risk of infection is relatively low, well under one in 1,000," he said.

"But if we see an infection in that setting, we want to think about MRSA strains, as well as atypical organisms such as *Mycobacterium chelonae* and *M. abscessus*." Both of these species of mycobacteria have poor response to typical fluoroquinolone monotherapy.

Cataract surgery. Mark Speaker's landmark study published in 1991[6] shed light on the central role of surface flora in intraocular infections, said Dr. Sheppard. "We learned that ocular surface contamination of the aqueous humor through the surgical wound was the main route for the development of endophthalmitis."

BEST PRACTICES AGAINST BAD BUGS

Despite a dearth of data, some simple practices may help keep infections at bay in ocular procedures.

Start with the surface. Dr. Sheppard recommends being fastidious about alleviating a patient's dry eye or blepharitis preoperatively. Both can predispose the patient to postoperative infection.

Copy Mr. Clean. Meticulous operating room technique and careful prep are fundamental for avoiding infections, said Dr. Flynn. Application of povidone-iodine (PI) for antisepsis provides broad, fast antimicrobial activity before ocular surgery or intravitreal injections: topical 5 percent PI for the conjunctiva and 10 percent PI for lids and lashes. It's also widely available at low cost.

Dilute effectively. Careful irrigation and aspiration to remove all residual debris and viscoelastic effectively dilutes any bacteria introduced into the anterior chamber during surgery, noted Dr. Sheppard. Frequent irrigation of the ocular surface also dilutes and removes potential pathogens.

Don't dabble. "Use antibiotics for a defined period at an effective dosage, then stop cold turkey," said Dr. Olson. "It's the slow dribbling of antibiotics over time that essentially guarantees that all you'll have left are very bad, very resistant organisms."

Reserve the big guns. "You don't always need to reach for the $100 bottle of antimicrobial," said Dr. Hwang. The CDC recommends reserving drugs like vancomycin for an established infection that's sight- or life-threatening. Dr. Olson added that, although still episodic, vancomycin-resistant staph are becoming less rare.

In the era of unsutured clear corneal incisions, said Dr. Sheppard, certain studies showed a two- to fivefold higher rate of postoperative endophthalmitis compared with current practice. Today, rates stand at between one in 1,000 and one in 5,000. "With a trend toward smaller incisions, we hope to see a continuous improvement in the infection rate," he said. Interestingly, he added, infection rates are lower for busier cataract surgeons and cataract centers. This could be related to perfected techniques, less risky practices, quicker surgeries, experienced operating room personnel, healthier patients and lower rates of capsular rupture.

IDENTIFYING THE RISKS

Given the overall low infection rates in ophthalmic procedures, it makes sense to focus on high-risk patients, taking extra precautions and performing cultures as needed to more carefully target the antimicrobial attack. But how do we identify where to focus our efforts?

Careful patient evaluation. A thorough risk assessment and exam can help guide the clinician's approach. For example, said Dr. Flynn, if a patient has conjunctivitis or a periocular infection, it's best to postpone the procedure until the condition has resolved.

Patients with diabetes or suppressed immunity, who have had previous ocular surgery, or who already have an exposed vitreous cavity through capsular disruption, as well as patients receiving an anterior chamber lens, are at increased risk of developing endophthalmitis, said Dr. Sheppard.

When to culture. In addition, Dr. Hwang recommended performing culture and susceptibility testing *prior* to initiating empiric therapy in patients with presumed infectious keratitis who have risk factors or clinical features that predict a potentially severe or recalcitrant infection, such as:

- Poor response to or noncompliance with previous antibiotic therapy
- Hospitalization or residence in a chronic care facility during the prior three months
- Risk factors for colonization with health care–associated MRSA (e.g., health care workers) or community-acquired MRSA (e.g., prisoners)
- Use of topical or systemic fluoroquinolones within the previous three months
- Previous documented or suspected ocular infection with MRSA or other antibiotic-resistant pathogens
- Compromised ocular surface or host immune function
- Previous corneal surgery or LASIK
- A corneal infiltrate that threatens or involves the central visual axis, exceeds 3 mm in diameter, is associated with hypopyon or threatens perforation.

In vitro vs. clinical susceptibility. The Clinical and Laboratory Standards Institute has formulated methods for testing the activity of antimicrobial agents against various bacteria and fungi, said Dr. Flynn. Its findings are valuable because they alert the clinician to the likelihood of in vitro and often-associated in vivo resistance. But are the laboratory findings borne out in clinical practice?

Although the correlation between in vitro and in vivo activity is quite good, said Dr. Olson, the route of administration plays a role in a drug's efficacy. For example, it's important to remember that you can achieve higher antibiotic levels on the surface of the eye. Thus, in practical terms, the organism may not appear to be resistant when treated on the surface, but "that same strain of bacteria inside the eye may indeed be very resistant," he said.

Dr. Hwang added that low laboratory resistance rates don't take into account the real-world effects of patient noncompliance—such as missing doses or using the medication longer than needed—which can *increase* the rates of resistance. It's also critical to remember that drug susceptibility profiles can differ from region to region and between patient subgroups.

Dr. Sheppard said that he routinely observes local microbiology lab reports, which confirm excellent staphylococcal sensitivity to aminoglycosides, such as gentamicin and tobramycin, polymyxin B, sulfamethoxazole and vancomycin. These sensitivities are generally conserved even when staphylococci become resistant to methicillin or oxacillin.

PROPHYLAXIS PROTOCOLS

Ophthalmologists employ a variety of overlapping but not identical preventive measures, making it difficult to design studies and draw conclusions about efficacy, said Dr. Hwang.

Intravitreal injections. At a 2004 meeting, experts on infectious disease and intravitreal injection reviewed protocols and developed guidelines to minimize complications for intravitreal injections, said Dr. Flynn. There was general agreement on 1) use of a lid speculum, 2) application of povidone-iodine (PI) to the ocular surface, eyelids and eyelashes, 3) avoidance of contact between the needle and eyelid margin or lashes and 4) avoidance of excessive eyelid manipulation.[7]

However, there was less agreement about the use of topical antibiotics before, during or after intravitreal injections, in part because of the poor penetration of topicals into the vitreous. Moreover, given the increasing frequency of intravitreal injections, said Dr. Flynn, repeated exposure of ocular

and nasopharyngeal flora to broad-spectrum topical antibiotics such as azithromycin and third- and fourth-generation fluoroquinolones may allow more virulent resistant bacterial strains to emerge.[8]

Topical fourth-generation fluoroquinolones before the day of injection have not been shown to reduce the rate of postinjection endophthalmitis, said Dr. Flynn, and demonstrate no added benefit in reducing conjunctival bacterial colonization beyond the effect of 5 percent PI alone.

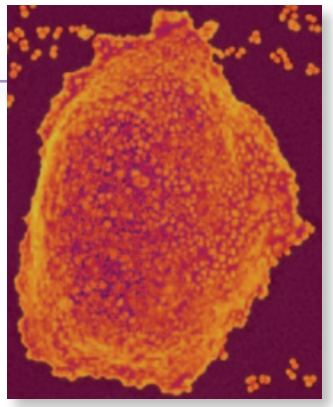
A recently published editorial coauthored by Dr. Flynn identified several advantages of antisepsis with PI over the use of prophylactic antibiotics for intravitreal injections: PI is substantially less expensive, provides broad-spectrum coverage and has a faster bactericidal rate. Perhaps most important, PI does not contribute to the worsening problem of antibiotic resistance.[9]

Dr. Hwang said that, if used, prophylaxis should be brief; a three-day perioperative regimen should be sufficient, and more than five days should never be necessary. "The major risk of infection is from microorganisms introduced during the injection, not after," he said. "The overlying conjunctiva heals rapidly and provides a substantial physical barrier to the further entry of organisms."[10]

Refractive surgery. "To my knowledge, we don't have any data that prophylactic antibiotics reduce the risk of infection after LASIK or that certain ones reduce risk more than others," said Dr. Hwang. "Yet, despite low rates of infection, we continue to use them due to concerns about rare but potentially sight-compromising infections."

Although the optimal prophylaxis regimen for LASIK is unknown, he said, its duration after surgery can be as short as three or four days. That's because the flap goes down immediately and is completely sealed within 24 hours, unlike procedures with larger incisions, where the potential for disruption of the epithelium poses a greater risk of postprocedure contamination.

Cataract surgery. "Until recently, there were no level 1 data in any prospective randomized analysis that a cer-



ROUGH ROAD FOR INTRACAMERAL THERAPY

The challenges of using intracameral antibiotics are clearly reflected in the Academy's recent survey of comprehensive ophthalmologists. Nearly eight in 10 do not use an intracameral antibiotic during cataract surgery. The rest put an antibiotic in the irrigating bottle or inject it into the anterior chamber at the end of surgery.

The latter is the preferred practice of Douglas D. Koch, MD, cataract surgeon and professor of ophthalmology at Baylor College of Medicine in Houston. He injects 1 mg of vancomycin in 0.1 cc of balanced salt solution at the end of every cataract procedure. He also uses topical preoperative and postoperative treatment with a fourth-generation fluoroquinolone.

"I think many more physicians would inject at the end of surgery if appropriate drugs were readily available," said Dr. Koch, "but we don't have unit dose syringes or preparations, so these antibiotics have to be mixed and drawn up, which requires a fair amount of effort. And if you get the concentration wrong by a power of 10, which can happen fairly easily, you turn a potential rare case of endophthalmitis into a whole day's worth of disastrous surgery," he said.

To reduce the risks of incorrect mixing, Dr. Koch follows a strict protocol that was developed by Howard V. Gimbel, MD, MPH. In addition to a two-step dilutional technique, his ambulatory surgery center has one nurse do the mixing and a second verify that it was done correctly.

A simpler approach is to inject preservative-free moxifloxacin into the eye, although this will be less effective against methicillin-resistant staph organisms. Alternatively, some surgeons put the antibiotic into the irrigating bottle, he said, but the data are not convincing, and there are questions about its efficacy because of dilution.

Although unit dose availability of these antibiotics may not be imminent due to cost-prohibitive FDA hurdles, Dr. Koch said that he sees more physicians turning to compounding or formulating pharmacies for this purpose. The downside? "This increases the cost of surgery," he said.

Dr. Koch is a consultant for Alcon.

CLINICAL INSIGHT. To better understand current practices on a number of topics, the Academy surveyed comprehensive ophthalmologists about how they would handle various clinical situations. Each month, *EyeNet* will feature one question—this month on antibiotics—and ask an expert to provide perspective on the response. In addition, the article will appear at www.aao.org/one with an accompanying online poll so that you can weigh in. Note that in the November/December issue, the survey's results will appear in News in Review.

tain practice has an absolute effect upon the rate of endophthalmitis," said Dr. Sheppard, "although level 2 data supported the effectiveness of preoperative PI with cataract surgeries.[11] Now, despite some controversy, the large European Society of Cataract and Refractive Surgeons (ESCRS) endophthalmitis study[12] provides level 1 data supporting postoperative intracameral cefuroxime." Regardless of antibiotic use, he said, the best advice is to control ocular surface inflammation and to carefully monitor patients who are potentially at higher risk.

Dr. Olson recommends applying PI before lidocaine jelly, which can block its effect, and then reapplying the PI before starting surgery. His prophylactic regimen includes 0.5 percent gatifloxacin eyedrops, four times daily, starting two days before surgery, with multiple drops applied just before surgery.

"I assume that everything on the surface of the eye is contaminated, particularly the conjunctiva," he said, explaining his extreme caution at every step of the procedure. "When I finish the case, if the incision doesn't seal easily and there is even a thought in my head that it may be less than a perfect wound, I'll put a suture in. I don't hesitate for a nanosecond."

Right after surgery, he applies a series of fourth-generation fluoroquinolones before the patient leaves; the drops are used every two hours for the rest of that day and then four times a day for a week. "That gets you good, high antibiotic levels," he said.

However, the effectiveness of postoperative topical prophylaxis remains debatable. "Once the epithelium has sealed the incisions," said Dr. Hwang, "the risk of subsequent postoperative microbial contamination into the anterior chamber is extremely remote."

Intracameral controversies. Despite the results of the large ESCRS trial showing the efficacy of intracameral cefuroxime in reducing the incidence of endophthalmitis, there is no standard in the United States regarding this approach, according to Dr. Sheppard. Whether—and how—this method is used varies widely between different countries and regions. (See "Rough Road for Intracameral Therapy," on the previous page, for results of an Academy survey.)

Dr. Hwang said that the choice of antibiotic is not clear, with most authors advocating for cefuroxime, some promoting vancomycin because of concerns about MRSA/MRSE, and others investigating the use of nonpreserved fluoroquinolones such as moxifloxacin. Dr. Flynn added that MRSA, *Enterococcus* and *Pseudomonas* have reduced susceptibility to cefuroxime.

"What we're lacking is a good single-dose intracameral antibiotic," said Dr. Olson. Some surgeons use nonpreserved topical drops as an intracameral injection, but topical formulations haven't undergone testing to ensure safety for that use. Dr. Olson predicted a move toward a belt-and-suspenders approach with staph-specific drugs: topicals to minimize surface contamination and an intracameral to ensure a supralethal dose in the anterior chamber.

Dr. Flynn is opposed to such an approach. He says that, in addition to concerns about increased resistance, the use of intracameral antibiotics carries the risk of contamination during mixing, toxicity from incorrect dosage and cystoid macular edema with certain antibiotics.

Irrigating solutions. To bypass the challenges of intracameral preparation and delivery, some surgeons simply add vancomycin to irrigating solutions, said Dr. Hwang. But this raises concerns

MEET THE EXPERTS

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about widespread exposure of periocular flora to a last-line agent against MRSA and MRSE.

"Furthermore, the relatively low concentration of vancomycin used in irrigating solutions, combined with the pharmacodynamics of vancomycin, renders this mode of delivery unfavorable for surgical prophylaxis," he said. "Vancomycin has a relatively short half-life in the anterior chamber [approximately two hours], yet killing occurs in a time-dependent fashion." Therefore, it makes more sense to use it in bolus form as an intracameral injection at the end of surgery. To achieve widespread adoption, he said, this approach would require a commercially available option, as well as studies supporting its safety and efficacy.

"An intriguing option for prophylaxis," said Dr. Flynn, "is the use of dilute povidone-iodine for constant surface irrigation during the surgical procedure." He pointed out a recent study that showed a significant reduction in anterior chamber bacterial contamination with use of a 0.25 percent PI irrigating solution.[13]

Other options. Dr. Hwang noted that some older drugs, such as trimethoprim–polymyxin B, may be excellent choices for perioperative ocular surface prophylaxis against MRSA and MRSE. Even today, he said, more than 90 percent of MRSA remain susceptible to the trimethoprim component of the combination.

"It doesn't penetrate well, so you can't rely upon it to achieve therapeutic levels in the aqueous against MRSA that have already entered the eye, but it can be helpful in intercepting MRSA on the ocular surface before it enters the eye."

Dr. Hwang has also used collagen shield delivery of high-dose cephalosporin into the eye for two decades. "You can get a level of delivery that is comparable to or better than subconjunctival injection, which can approximate the effect of an intracameral cephalosporin injection."

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