MRSA – the rising menace

Nick Lane PhD

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is emerging as the leading cause of poor visual outcomes after both cataract and refractive surgery. With recent studies showing growing resistance to fourth-generation fluoroquinolones, *EuroTimes* asks what ophthalmologists can do about it.

A decade ago, MRSA was an arcane threat – worrying, but restricted mainly to intensive care wards. But according to a study published in *JAMA* last October, by the Centers for Disease Control and Prevention (CDC), MRSA is now a bigger killer than AIDS, with nearly 20,000 deaths a year attributed to it in the US.

And MRSA is no longer restricted to immunocompromised patients. Last year, APIC – the Association for Professionals in Infection Control and Epidemiology – reported that MRSA was eight times more prevalent in US hospitals than had been thought, with an infection rate of about five per cent. Nearly 70 per cent of hospital *Staphylococcus* infections are now multiple drug-resistant MRSA.

In a follow-up survey of more than 2000 infection specialists reported this June, 76 per cent said their hospitals had taken steps to prevent MRSA transmission in the last year, but 54 per cent said that not enough was being done.

Worse, MRSA has left hospital and invaded the community. Strains such as USA300 have been linked with outbreaks in sports teams and clubs (the first being a British rugby team in 1998) as well as prisons, families, schools and other locations where people come into close contact.

The common denominator seems to be skin abrasions, turf burns or other minor wounds. One outbreak, for example, was traced to a local unlicensed tattoo artist. Skin infections are easily mistaken for spider bites.

The carriage rate of MRSA in the population is startling. A 2004 study showed a carriage rate of about 20 per cent. Four years on, that rate is now close to 50 per cent, according to Francis Mah MD, at the University of Pittsburgh and co-medical director of the Charles T Campbell Ophthalmic Microbiology Laboratory.

The figures are very similar in Europe. According to a 2006 review in *The Lancet* from the EARSS (European Antimicrobial Resistance Surveillance System) the prevalence of MRSA in Western Europe and the US is equivalent, with the carriage rate in the UK, Ireland, France, Spain and Italy at 25 to 50 per cent, with only slightly lower rates in Germany and Eastern Europe.

Rates are lower in Holland and Scandinavia, but MRSA is on the rise there too.

Not surprisingly, ophthalmologists are beginning to reap the whirlwind.

The eyes to the wrong

At Cornea Day, preceding the ASCRS conference in Chicago this April, Terry Kim, MD, of the Duke Eye Centre, Durham, North Carolina, presented the results of an ASCRS-sponsored survey of infectious keratitis.

The first report of MRSA causing keratitis was as recent as 2001, yet according to the survey, in 2007 as many as 61 per cent of cases were caused by *Staphylococcus* infections. The incidence of mycobacterial infection, in contrast, has fallen.

"MRSA is now the single most common infection occurring after LASIK and surface ablation procedures," Dr Kim concluded. The risk of infection, he noted, was significantly greater with surface ablation and keratome use than with LASIK and femtosecond lasers.

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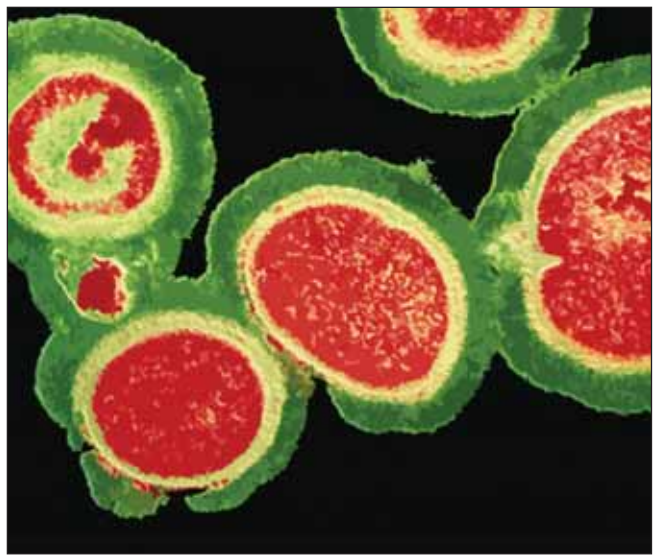
>
> **Vahid Feiz MD**

It's a similar story after cataract surgery. The incidence of endophthalmitis has been rising for more than a decade – a trend that has paralleled the widespread adoption of clear corneal incisions – but as in keratitis, there has been a change in the spectrum of causative organisms.

According to a retrospective study published in the *AJO* this March by Vincent Deramo MD, and colleagues at Long Island Vitreoretinal Consultants and the Albert Einstein College of Medicine, MRSA infection accounts for around 18 per cent (six of 33 culture-positive cases) of acute endophthalmitis referred to their vitreoretinal practice over three years.

Dr Deramo notes that, despite the small size of their study, the incidence of endophthalmitis caused by MRSA appears to have grown substantially since the Endophthalmitis Vitrectomy Study was published in 1996, when MRSA was reported in just six of 323 isolates (1.9 per cent).



Even more seriously, visual outcomes with MRSA were poor in four of these patients (67 per cent), with visual acuity at last follow-up being no light perception in two eyes, and hand movement in two eyes.

"That's a much worse outcome than the 'typical' patient with coagulase-negative Staphylococcus endophthalmitis – still the most common pathogen – many of whom regain 20/40 or better vision if treated early," Dr Deramo told *EuroTimes*. "In addition, most of our MRSA patients had serious corneal involvement as well, which is uncommon in endophthalmitis."

Vahid Feiz MD, of UC Davis Medical Centre, has reported similar experiences. "There is a consensus now that MRSA can be more aggressive and damaging to the eye than some of the other infections. This is especially true of endophthalmitis after ocular surgery," he told *EuroTimes*.

Courting resistance

As recently as 2004, Dr Mah could write in a review (Curr Opin Ophthalmol) of the fourth-generation fluoroquinolones moxifloxacin and gatifloxacin, "Gatifloxacin has equal efficacy when compared with vancomycin against methicillin-resistant and fluoroquinolone-resistant *Staphylococcus aureus* in a rabbit model. Gatifloxacin actually had superior clinical scores compared with vancomycin."

He also noted that the fourth-generation fluoroquinolones have "a delayed propensity to the development of bacterial antibiotic resistance." These virtues were instrumental in the widespread adoption of fourth-generation fluoroquinolones by ophthalmologists.

Yet by 2006 Dr Deramo and others were already reporting serious resistance to gatifloxacin and moxifloxacin. In a retrospective consecutive series of 42 eyes with acute endophthalmitis, 74 per cent (31 eyes) had been treated with perioperative gatifloxacin or moxifloxacin – and 57 per cent (24 eyes) were still taking one of these antibiotics at the time of diagnosis.

In his 2008 *AJO* paper, Dr Deramo noted that in all six cases of MRSA endophthalmitis, the patients had been started on fluoroquinolone antibiotics two or three days before surgery.

And Dr Deramo's worrying findings have recently been corroborated by the Ocular TRUST Study (Tracking Resistance in US Today), reported in the *AJO* this June. While confirming the broad efficacy of fluoroquinolones in general, including gatifloxacin and moxifloxacin against MSSA, *S. pneumoniae*, and *H. influenzae*, the TRUST group reported poor efficacy against MRSA.

In 197 ocular isolates of *Staphylococcus aureus*, MRSA susceptibility to fluoroquinolones was just 15.2 per cent, right across the class. An alarming 76 per cent and 82 per cent of ocular MRSA isolates were resistant to moxifloxacin and gatifloxacin, respectively.

The authors concluded, "High-level in vitro MRSA resistance suggests the need to consider alternative therapy to fluoroquinolones when MRSA is a likely pathogen." But it should be noted that ophthalmologists are not the villains here – it's the scandalously widespread use of fourth-generation fluoroquinolones in animal husbandry that is at fault.

The only agent tested in the Ocular TRUST Study that retained high efficacy against MRSA was trimethoprim, which was effective in 94 per cent of cases, although it was less effective against *S. pneumoniae*, and *H. influenzae* than the fluoroquinolones.

Ironically, the antibiotic that has long been at the centre of controversies in ophthalmology, vancomycin, has also retained good efficacy against MRSA, according to both Dr Deramo and Dr Feiz, although periodic cases of resistance have been reported. Unfortunately, vancomycin is not being tested in the TRUST Study.

In 1995, the CDC recommended against routine prophylaxis with vancomycin, in an effort to halt the spread of resistance, a recommendation habitually ignored by

Peter Barry

Terry Kim

ophthalmologists. Even in 2006, a survey of ASCRS members by Samuel Masket MD, Jules Stein Eye Institute, Los Angeles, indicated that some 18 per cent of cataract surgeons in the US continue to use intracameral vancomycin after cataract surgery.

Peter Barry MD, Dublin, chairman of the ESCRS Endophthalmitis Study Group, told *EuroTimes* that as many as 60 per cent of Americans who receive an infusion of antibiotics for prophylaxis receive vancomycin.

In 1999 and again in 2005, the CDC issued a politely worded joint statement with the AAO, advocating that "prudence, and perhaps even restraint, should be exercised in the selection of appropriate antimicrobial agents" – again recommending against the routine prophylactic use of vancomycin in hospital settings (but not necessarily in outpatient clinics), while conceding there is no evidence that ophthalmologists have encouraged resistance through their less-than-restrained use.

The irony deepens. In place of vancomycin, the AAO/CDC joint statement recommends the use of povidone-iodine antisepsis – which is in any case practically universal as the standard of care – and the perioperative use of broad-spectrum topical antimicrobials, with an activity spectrum that includes both Gram-positive and Gram-negative bacteria.

Presumably they had in mind something like the fourth-generation fluoroquinolones.

But now gatifloxacin and moxifloxacin are losing activity against MRSA, while vancomycin, overused prophylactically by ophthalmologists, has retained its efficacy.

Given the inexorable rise in MRSA infections and their poor ophthalmic outcomes, what's the best policy now? A surprising place to look may be the ESCRS Endophthalmitis Study, which examined precisely none of these questions.

There's been a degree of ambivalence about the ESCRS Study, with a split emerging between the Europeans and the Americans about the use of intracameral cefuroxime.

Dr Barry and colleagues have argued that the five-fold reduction in endophthalmitis proves that intracameral cefuroxime should be considered the gold standard. American ophthalmologists like Dr Randall Olson MD, at the University of Utah, have criticised the narrow spectrum of activity of cefuroxime, its potential for allergic reactions, and the lack of unit-dose packaging or FDA or indeed EMEA approval for intracameral injection.

The high rate of endophthalmitis in the control groups also troubles many ophthalmologists, including Dr Barry, although Dr Olson suspects that the true incidence of endophthalmitis is likely to be much higher than most ophthalmologists suspect.

But whatever the optimal antibiotic regimen may be, an important, if less appreciated, aspect of the study was the rate of MRSA endophthalmitis – zero, according to Dr Barry, despite the large study population of more than 16,000 patients.

That's not because any of the antibiotics were effective against MRSA, because they probably weren't. Even levofloxacin, a third-generation fluoroquinolone given topically in the study, is broadly inactive against MRSA, with 79 per cent resistance, according to the Ocular TRUST Study, right up there with gatifloxacin and moxifloxacin.

And it probably wasn't because MRSA is less of a threat in Europe. The 24 ESCRS Study centres were in Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey and the UK – all with MRSA rates broadly comparable to the US.

Dr Barry believes the absence of MRSA in the ESCRS Study was attributable to the rigorous exclusion criteria applied in the study, which excluded patients from nursing homes and other settings where MRSA is rife.

While this probably artificially lowered the 'real' rate of endophthalmitis even further, there is another important take-home lesson here – the risk of MRSA can be identified in advance and dealt with accordingly. Screening works.

"We apply the same criteria in my own practice," Dr Barry told *EuroTimes*. "We screen all patients at high risk of MRSA and they must have three consecutive negative swabs before we go on to surgery."

Dr Feiz agrees that rigorous screening of high-risk patients is imperative. He cites the highest risk groups as healthcare workers, chronically ill patients, anyone hospitalised recently or in long-term care facilities, patients with poorly controlled diabetes or on renal dialysis, and any patient with a history of MRSA at any site.

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These patients are likely to be colonised with MRSA", Dr Feiz told *EuroTimes*. "The usual site of colonisation is the nose." In addition to the standard preoperative antisepsis, notably povidone-iodine, Dr Feiz notes that community-acquired MRSA is still usually sensitive to trimethoprim (a view confirmed by the Ocular TRUST Study) and chloramphenicol drops.

Timing is also very important. For example, in the ESCRS Study, Dr Barry notes there was a standard preoperative antisepsis regimen – "Povidone-iodine had to be applied for three minutes," he told *EuroTimes*. "And I mean three minutes – we timed it."

Other preventive measures include mupirocin ointment, available as a nasal ointment, which eliminates MRSA in 91 per cent of colonised healthcare workers within two to four days. If that fails, a second option is linezolid, an oral medication with excellent MRSA coverage.

"It has wonderful penetration into the eye after two oral dosings", Dr Feiz told *EuroTimes*, "and there is also some animal work looking at linezolid eye drops. Very promising." He recommends that preoperative oral linezolid be considered in patients at high risk of MRSA infections.

So what about vancomycin? Should it be used prophylactically or reserved for treatment? Drs Barry, Feiz and Deramo are all in broad agreement here: treatment only.

"I never recommend prophylactic use of vancomycin." Dr Deramo told *EuroTimes*. "I would reserve it for treatment only. We're in big trouble if resistance develops to vanco...."