The Alphabet Soup of Superbugs

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The concern for antibiotic resistant microorganisms continues to grow with estimates of over two million people getting resistant infections annually in the United States, and over 20,000 deaths each year directly attributed to these infections.[1] Inappropriate use or overuse of antibiotics is the single most important factor in the emergence of antibiotic-resistant pathogens. In 2013 the CDC published a report describing the top 18 drug-resistant threats to the United States and in 2015 the White House released the National Action Plan to Combat Antibiotic Resistant Bacteria. Notable pathogens of concern that would be of interest to eye banking professionals include methicillin-resistant staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), multidrug-resistant acinetobacter (MDR-A), multidrug-resistant pseudomonas, extended-spectrum enterobacteriaceae (ESBL), and carbapenem-resistant enterobacteriaceae (CRE). The emergence of more pan-resistant pathogens worldwide, such as the mcr-1 colistin resistant *Eschericha coli*[2]highlight our need to be informed, especially given the impact of multidrug-resistant pathogens in the field of transplantation. Bacteria frequently considered to be non-pathogenic or normal flora may with the acquisition of resistance plasmids or mutations, become organisms of significant concern especially in immunocompromised hosts or in screening hospitalized potential donors. Familiarity with these organisms and or the use of antibiotics associated with resistant pathogens will enable the initial reviewer of medical history to more efficiently and effectively evaluated the suitability of a potential donor for transplantation.

Although ocular tissue, due to its avascular nature, is usually not affected by many of the hospital acquired infections, FDA regulatory requirements and industry standards must also be considered along with potential risk in making donor eligibility/suitability decisions. As eye banking professionals screen potential donors and review medical records for signs of possible transmissible infection, it is important to know what microorganisms and what antibiotics should raise "red flags" due to the changing resistance patterns in their local hospitals and medical facilities, as reported in the hospital antibiograms. The following is a review of the current profiles of those "Superbugs" that may be of concern in tissue transplantation, and the antibiotics which may be utilized to treat them. In review of medical records it is important to determine the reason for prescribing antibiotics — prophylactic, administration versus specific targeted treatment, and to identify any positive cultures (blood, urine, sputum, wound, etc).

Methicillin-resistant staphylococcus aureus (MRSA)

The first wide-spread initially hospital acquired "Superbug" was MRSA, emerging in the 1960s, driven by antibiotic use, hemodialysis, intensive care, and increased MRSA colonization. It is one of the leading causes of surgical site infections and contributes to nosocomial bloodstream infections and pneumonias. However community-associated MRSA infections causing skin and soft tissue infections in those patients without the traditional risk factors for MRSA emerged in the 1980s in IV drug users, with risk factors now being men who have sex with men, HIV-infected, sports teams, and prison inmates and guards. Currently the distinctions between the two are now blurred as more community-acquired strains are seen in the hospital setting, and hospital-acquired resistance patterns are increasingly noted in the community. The conventional antibiotic of choice has been vancomycin, however vancomycin-intermediate (VISA) or vancomycin-resistant (VRSA) strains have been reported since the 1990s, associated with prolonged vancomycin exposure. The first case of VRSA in the United States was reported in 2002 in Michigan.[3] Antibiotics used to treat VISA/VRSA bacteremias include daptomycin, ceftaroline, linezolid, and telavancin. For other skin and soft tissue infections or intraabdominal infections, dalbavancin, oritavancin, tigecycline, and quinupristin-dalfopristin may be considered. Finally, a new fluoroquinolone (delafloxacin) has been approved for MRSA skin and soft tissue infections.[4]

Vancomycin-resistant enterococcus (VRE)

The development of VRE arose through the use of glycopeptides such as avoparcin in the animal feed industry,

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leading to its emergence in Europe in the 1980s. In the hospital setting, VRE (mostly *Enterococcus faecium*) colonization usually precedes infection, which is driven by host factors such as vancomycin or cephalosporin use, prolonged hospitalization, end-stage renal disease requiring dialysis, cancer, transplant recipients, ICU stay or invasive devices. In addition to rising vancomycin resistance, studies show increased mortality in patients infected with VRE as compared to vancomycin-susceptible strains[5]. Antibiotics that are effective for the treatment of VRE include daptomycin, linezolid, oritavancin, tigecycline, quinupristin-dalfopristin, and telavancin, sometimes in combination with gentamicin, ceftriaxone, rifampin, minocycline, ampicillin, or ciprofloxacin, depending on the site of infection and the susceptibility of the isolate.

Multidrug-resistant acinetobacter (MDR-A) and pseudomonas

Acinetobacter and pseudomonas are gram-negative bacteria commonly found in soil and water, but can colonize humans in wounds or tracheostomy sites. MDR-A and MDR-pseudomonas are resistant to more than three classes of antibiotics, including the penicillins or carbapenems (MDR-A) and are associated with patients exposed to health care settings, who have underlying diseases such as diabetes, severe burns, immunocompromised states, or have intravascular catheters. Infections with these pathogens include bacteremias, urinary tract infections, meningitis, and wound infections, with higher mortality rates. Therapeutic options consist of aminoglycosides such as tobramycin, polymyxins (such as colistin), tigecycline, combination cephalosporins (ceftazidime-avibactam or ceftolazone-tazobactam), carbapenems such as meropenem or doripenem (MDR pseudomonas), and minocycline, either as monotherapy or more often in combination depending on the susceptibility profile of the isolates.

Extended-spectrum enterobacteriaceae

Extended-spectrum beta lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics including piperacillin-tazobactam, cephalosporins, and aztreonam. There are numerous enzymes that confer resistance to these antibiotics (TEM, SHV, CTX-M, and OXA) with different enzymes selecting out particular antibiotics. ESBL pathogens including Klebsiella and *Eschericia coli*, emerged in the 1980s with cefotaxime use[6] and now are found worldwide, with high prevalence in Asia, Latin America, and the Middle East. Of particular note is the rising prevalence in pediatric infections. Risk factors include hospitalization, long term care facility residence, hemodialysis, intravascular catheter use, recent antibiotics, steroids, or percutaneous feeding tubes. Treatments of choice include the carbapenems such as ertapenem, meropenem, imipenem, and doripenem. The new combination cephalosporin-beta-lactamase inhibitors such as ceftolazone-tazobactam and ceftazidime-avibactam may be effective in select cases, and polymyxins, fosfomycin, ciprofloxacin, or aminoglycosides such as amikacin or tobramycin may be used depending on the site of infection and the susceptibility profile.

Carbapenem-resistant enterobacteriaceae (CRE)

CRE include *Eschericia coli*, Klebsiella, and Enterobacter, contain carbapenem-hydrolyzing beta lactamases that confer resistance to carbapenems. Infection with these bacteria can end in death in 50% of the patients who acquire these infections in hospitals or other healthcare facilities. CRE first appeared in the 1990s, with rising prevalence worldwide. Klebsiella pneumonia carbapenemase (KPC) and New Delhi Metallo-beta-lactamase (NDM) are types of CRE, with the more recently emerged mcr-1 colistin resistant *E. coli* of particular concern. Risk factors for CRE infections include care in long –term care facilities, hospitals, or nursing homes, use of antibiotics, mechanical ventilation, organ transplantation, indwelling catheters, malignancy, and diabetes. CREs cause pneumonias, bloodstream infections, urinary tract infections, abdominal infections, and surgical site infections. Antibiotics utilized in the treatment of CREs include polymyxins, tigecycline, and the cephalosporin combinations (ceftazidime-avibactam), especially in combination.

Overuse of antibiotics,extended stays in hospital and long term care facilities, and presence of intravascular catheters, coupled with patients with co-morbidities such as diabetics, end-stage renal disease on dialysis, or cancer, have led to the emergence and rapid dissemination of multidrug-resistant bacteria. Patients with prolonged stays in the hospital are susceptible to infections with these pathogens, developing pneumonias, bacteremia, urinary tract infections, and skin and soft tissue infections. While a documentation of sepsis will disqualify a potential donor, recognition of the antimicrobials used to treat these infections may alert the eye banking professional that the donor may be infected with one of these “Superbugs”, with implications for the transplantation. In addition as long term hospitalization and the associated volume of the medical record, either electronic or paper, make it more difficult for the initial review to ascertain the relevant medical information, including sepsis, knowing the microorganisms and antibiotics which may be the most significant in host infection and possible

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sepsis is a benefit to the eye bank technical personnel in their search for relevant medical history. This familiarity with the antibiotics most frequently associated with treating resistant organisms will allow the reviewer to focus on locating charting and laboratory tests for infection. Based on microbial changes and drug treatment regimes, the careful medical record review may then necessitate the eye bank professional to consult the attending physicians, infectious disease specialists and of course medical director, to appropriately evaluate and reach a conclusion on suitability of potential donors health history and recent medical risk factors or to correctly determine the donor unsuitable due to infection or sepsis.

Table 1. *Antibiotics for the Treatment of Multidrug-resistant pathogens*

Generic name	Brand name
Amikacin	Amikin
Ampicillin	Omnipen, Polycillin, Principen, Totacillin
Ceftaroline	Teflaro
Ceftazidime-avibactam	Avycaz
Ceftolazone-tazobactam	Zerbaxa
Ciprofloxacin	Cipro, Ciproxin
Colistin	Coly-mycin M
Dalbavancin	Dalvance
Daptomycin	Cubicin
Delafloxacin	Baxdela
Doripenem	Doribax
Ertapenem	Invanz
Fosfomycin	Monurol
Gentamicin	Garamycin, G-Mycin, Jenamicin
Imipenem	Primaxin
Linezolid	Zyvox
Meropenem	Merrem
Minocycline	Dynacin, Minocin, Monodox
Oritavancin	Orbactiv
Polymyxin B	Polymyxin B
Quinupristin-dalfopristin	Synercid
Rifampin	Rifadin
Telavancin	Vibativ
Tigecycline	Tigacyl
Tobramycin	Nebcin

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