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Review Article

Burden of Post-Operative Infections and Methicillin-Resistant Staphylococcus Aureus (MRSA)

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Infections after surgical procedures can cause pain, poor wound healing, and increase the need for further treatment including antibiotics, longer hospital stays, and health care costs. Post-operative infections are a major cause of such increased mortality and morbidity around the world, especially in developing countries. Annually direct and indirect cost estimates of post-operative infections are more than $1 billion and $10 billion, respectively [1]. Often, major post-operative infections are reported as a surgical site infection (SSI) which has been defined by the CDC as an infection occurring within 30 days of an operative procedure or within one year in the event of implanting a device/material. These infections can be further classified as [1]:

- Superficial (confined to the skin and subcutaneous tis sues around the incision).
- Deep (involving the fascia, muscle, bone, or implant).

The most common causative organism involved with SSIs is Staphylococcus aureus (S.aureus). A recent epidemiologic study reported that in adults, 50% to 80% of SSI isolates are pure S.aureus [1]. Gram-negative organisms are more common in immunocompromised hosts such as people with diabetes and intravenous drug abusers [1]. Other risk factors for developing a postoperative infection include; obesity, older age, emergency operations, obvious contamination (with debris, pus, stool, or other substances) of the injury or the surgical area [2].

Sequalae of postoperative infections may include failure of the surgical procedure, sepsis, organ failure, and even death. There are several ways to prevent these types of infections which include; prophylactic antibiotics, using an antiseptic solution to "prep" the area around a surgical incision when appropriate; maintaining sterility of the surgical field and operating tools [3].

However, some bacteria are resistant to routine antibiotics, for example, methicillin-resistant Staphylococcus aureus (MRSA). It can be defined as an oxacillin minimum inhibitory concentration (MIC) of greater than or equal to 4 micrograms/ml. MRSA can either be:

- Hospital acquired (HA)
- Community acquired (CA)

Since it was first discovered in 1961, several outbreaks of MRSA have been reported since the 1970s. There has been significant literature published associating MRSA infections with significant morbidity, mortality, length of stay, and cost burden. MRSA occurs by mutation of a penicillin-binding protein, a chromosome-encoded protein. This type of resistance is transferred between S. aureus organisms by bacteriophages, which is one of the only medically relevant examples of chromosome-mediated drug resistance by phage transduction mechanism.

MRSA infection can occur in wounds (SSIs), the chest, or bloodstream (bacteremia). Its incidence varying from 1% to 33% depending upon several factors such as, type of surgery performed, carrier status of the individual. Other risk factors include

- Open wounds
- Hemodialysis or other long-term catheterizations
- Immunocompromised conditions (ex: HIV)
- Advancing age (< 65 years)
- Living in an area with a high prevalence of CA-MRSA or admission to a hospital with a high prevalence of HA-MRSA
- Surgeries involving indwelling implants and prostheses.

In the United States, MRSA's caused a caused an estimated 125,000 hospitalizations annually, while in European Union member states, smaller countries like Norway, and Iceland, MRSA infections cause an estimated one-million extra hospital stays and cost an estimated 600 million euros annually. Its associated in-hospital mortality rate is estimated at 12.9% as compared to 3% in those not hospitalized. The optimal treatment involving antibiotics is still not known, despite immense research. Thereby, making it a life-threatening condition and cause extended hospital stays.

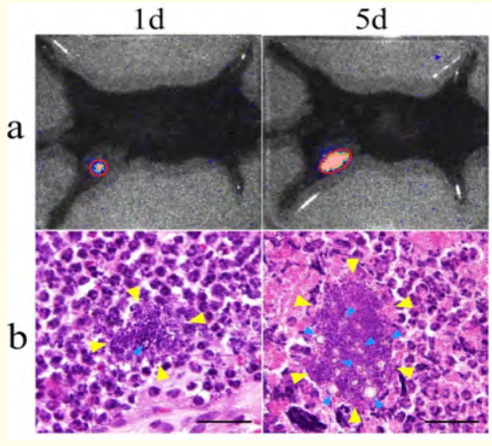

Figure 1: *Histopathology of MRSA infections in an arthritis model on day 1 and 5.*

(Image source: https://openi.nlm.nih.gov/detailedresult.php?img=PMC3383702_pone.0039823.g002&req=4).

Diagnosis and Evaluation

Clinical suspicion in patients with risk factors related to MRSA infection is crucial in diagnostic and therapeutic intervention. Samples of suspected sources of infection can be collected from blood, sputum, urine, or wound scraping for analysis including. DNA polymerase chain reaction (PCR) of MRSA is the most sensitive test and gold standard test if cultures are inconclusive. DNA PCR of MRSA from nares is a frequently employed diagnostic test to rule out MRSA colonization. It is not a confirmatory test of MRSA infection, but a negative test is highly sensitive to rule out MRSA infection. Sputum cultures are not very specific or sensitive to diagnose MRSA pneumonia, therefore bronchoalveolar lavage or a deep tracheal aspirate for intubated or tracked patients can be performed. A positive Gram stain with cocci in clusters is suggestive of *S. aureus.*

Treatment/Management

Antibiotic substance can be defined as one of a class of substances produced by living organisms that is capable of destroying, or inhibiting the growth of, micro-organisms, and is especially used for therapeutic purposes. Synthetic organic compounds that have similar properties are also called antibiotics. A variety of antibiotics, including beta-lactam (penicillin derivatives, cephalosporins), glycopeptide antibiotics (e.g. vancomycin, teicoplanin), clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), tetracyclines (doxycycline or minocycline), linezolid, daptomycin, telavancin, rifampicin, gentamycin, and fluoroquinolone, can be used for the treatment of MRSA. Considering antibiotic resistance of MRSA, a combination of antibiotics is administered as a single agent or in combinations, prophylactically, during operations, or postoperatively in different ways, with the common routes being oral, intravenous, and topical administration.

The selection of an empiric antibiotic therapy for the treatment of MRSA infection depends on factors such as

- The type of disease
- Local *S. aureus* resistance patterns
- Availability of the drug
- Side effect profile
- Individual patient profile.

For most SSI's empirical treatment is provided with oral antibiotics like trimethoprim/sulfamethoxazole, tetracyclines, such as doxycycline or minocycline, and clindamycin. Newer agents, such as linezolid and tedizolid, and delafloxacin also can be used as alternative oral regimens if available and deemed cost-effective. Parenteral antibiotics are indicated for invasive SSTIs or with signs of systemic involvement, inadequate response to oral therapy, or if an SSTI occurs adjacent to an indwelling device. Intravenous vancomycin is the drug of choice for most MRSA infections seen in hospitalized patients. It can be used both as an empiric and definitive therapy as most MRSA infections are susceptible to vancomycin. The dosage depends upon the type and severity of the infection. Vancomycin trough is usually obtained just before the fourth dose to ascertain a therapeutic level. The goal trough range typically ranges between 10 and 20 micrograms/ml. For complicated infections, the goal trough is between 15 and 20 micrograms/ml. The dose should be adjusted based on trough levels in the serum and according to renal function. Daptomycin is a suitable parenteral alternative when vancomycin is not available or not being tolerated. Other short-acting options include ceftaroline and telavancin. Long-acting treatment options include dalbavancin and oritavancin. Regardless of the initial empiric antibiotic choice, subsequent therapy should be tailored based on the careful review of culture and susceptibility data.

The duration of therapy for treatment of MRSA SSTIs may range from 5 to 14 days depending on the extent of infection and response to treatment [4].

For Bacteremia source control is a significant part of the treatment for MRSA bacteremia along with empiric MRSA coverage until the susceptibility results are available. Vancomycin and daptomycin are considered adequate empiric therapy according to the Infectious Diseases Society of America guidelines of 2011. MRSA

isolates in the bloodstream with vancomycin MIC greater than or equal to 2 micrograms/mL may not respond adequately to vancomycin. Therefore, in these cases, daptomycin is a better option or a combination parenteral drug regimen can be used, such as the following [2]:

- Daptomycin plus ceftaroline or other beta-lactams
- Vancomycin plus ceftaroline or other beta-lactams
- Daptomycin plus trimethoprim-sulfamethoxazole
- Ceftaroline plus trimethoprim-sulfamethoxazole.

Teicoplanin is a bacteriostatic glycopeptide with a similar spectrum of activity and efficacy as vancomycin and is better tolerated than vancomycin. However, it is used less commonly due to its limited availability. Linezolid is another suitable alternative for MRSA bacteremia especially in cases of vancomycin insensitive or vancomycin-resistant S. aureus. It has a narrow therapeutic range with a higher incidence of nephrotoxicity than vancomycin. Other newer agents for the treatment of MRSA bacteremia include telavancin, dalbavancin, and oritavancin. Persistent, positive cultures after 48 hours of treatment should prompt further evaluation related to drug susceptibility and source control. Follow-up cultures should be repeated to document the clearance of the infection from the bloodstream.

Other treatment measures include [3]:

- Re-exploration of a surgical incision to drain pus, an ab scess (a collection of infected fluid), or a hematoma (an area of blood and blood clot that can also become infected)
- If hardware is involved (such as plates, screws, or total joint replacements), and the infection is seri ous, the metal parts may need to be removed
- Supportive care, including fluids, medications to lower a fever, and pain medication, is often needed

Preventing postoperative infection

There have been several measures employed as an effort to reduce postoperative infections and improve overall health care quality. Some of the steps recommended, were [3,5]:

- Appropriate choice of preoperative antibiotics
- Proper timing and duration of antibiotic dosing
- Clipping of hair (instead of shaving) around a surgical in cision site
- Hand hygiene means washing hands with soap and wa ter or an alcohol-based cleanser before and after contact with patients who have MRSA infection
- Contact precautions include the use of gowns, gloves, and possibly masks during clinical encounters with patients with MRSA infection
- Keeping appropriate blood sugar levels for persons with diabetes (especially for individuals having heart surgery)
- Keeping patients having colon surgery at a normal body temperature
- Isolation of patients who have an MRSA infection
- Significant evidence suggests that implementation of hand hygiene and antimicrobial stewardship interven tions effectively reduce MRSA infection rate.

Conclusion

Post-operative and MRSA infections are a major public health concern in many countries around the world for hospital and community acquired infection. However, a decline in these infections has been observed which can be contributed to implementation of safety protocols and control interventions. Despite decline in rates of post-operative infections, measures need to be continually implemented for eradicating these infections. Therefore, continuous surveillance of antibiotic resistance, implementation of antibiotic stewardship, and infection control interventions are recommended.

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