Management of culture-negative surgical site infections

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Abstract
Infections at the surgical site delays wound healing, prolongs hospitalization, increases morbidity and the overall costs. These issues are compounded when the postoperative infection is culture-negative. This article outlines the general principles of managing postoperative surgical site infections, with an emphasis on culture-negative infections. Practical issues, in the absence of positive culture are discussed, together with practice points to minimize the incidence of culture-negative surgical site infections.

Key words: surgical site infections, Gram positive, Gram negative, bacterial culture, culture negative SSIs

Surgical site infections (SSIs) are defined as infections of skin or underlying soft tissues at the surgical site, following an operation. These are common postoperative complications. Their incidence varies, but is more common following emergency surgical procedures. SSIs are associated with tissue destruction up to varying depths, delay or even failure in wound healing, disfiguring or disabling scars, persistent or recurrent pain at the operated site, bacteremia, pyrexia, and incisional hernias.

In addition, they also prolong the hospital stay and increase the costs.

This article is an overview of the management of surgical site infections with emphasis on culture negative SSIs. For a detailed review, please refer to the published literature\(^1\)\(^-\)\(^3\) and to the articles listed in the further reading* section.

Management of SSIs is based on structured protocols, which are as follows:

i. Appropriate preoperative management, which include assessment and optimization of various risk factors (Table 1).

ii. Initiation of antibiotic prophylaxis to cover the common pathogens causing SSIs (Table 2).

iii. Control of operating theater environment and avoidance of hypothermia.

iv. Appropriate intra-operative management of the tissues and incision.

v. Appropriate postoperative management which include optimization of hyperglycemia, supplemental oxygenation, judicious use of blood transfusion, nutritional support with emphasis on early enteral nutrition.

The incidence of SSIs can be reduced significantly with these evidence-based protocols\(^1\)\(^-\)\(^2\). Despite the efforts, 2 to 10% of all elective surgical cases do develop SSI. Further management of such infected wounds is simplified to a certain extent by the culture and sensitivity reports, by remaining updated with the current hospital microbiological data and by administration of nutrition supplements which facilitate wound healing. Such attempts may limit the prolonged hospital stay and will also reduce the costs\(^3\).
A common problem is managing a patient with all the clinical signs of surgical site infection, but with “no bacterial growth” on the culture report! The incidence of such ‘culture negative SSIs’, based on published studies can be up to 30%5,6.

Many micro-organisms (Table 3) and non-infective factors (Table 4) are responsible for causing culture negative surgical site infections.

### Culture negative SSIs

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### Modes of inoculation of microbes causing culture negative SSIs

There are three ways by which surgical sites can get infected.

1. Intraoperative inoculation of the surgical wound from non-sterile instruments and contaminated prosthetics and even surgical solutions. Clinical examples are *Legionella* species and rapidly growing mycobacteria, etc.
2. Improper cleaning of surgical site by an inappropriate surgical solution. Clinical examples are *Staphylococcus epidermidis, Mycoplasma species*, etc.
3. By blood-spread, in the postoperative period. Clinical examples are *Mycoplasma species*.

### Causes of culture negative SSIs

Various agents have been hypothesized as causes for culture negative infection at surgical sites:
1. The most frequent cause is thought to be due to culturing the infected site after commencement of antibiotics.
2. Atypical organisms do not grow on standard culture media. Also they may grow rather slowly and the culture plates are discarded before the growth becomes apparent.
3. Common contaminant like *Staph. epidermidis* are generally ignored as contaminants, but may actually be the cause of postoperative infection.

### Role of microbiologist in detecting SSIs

The standard practice is to incubate the culture material (from infected surgical sites) for 48 hours. If no growth is seen, these plates are discarded and the result is reported as ‘no growth’ or ‘culture negative’. In such instances, the microbiologist should be aware of some organisms might be missed, especially if the culture plates are discarded soon after 48 hours. Alternately, some of the colonies are quite small and might be missed, if not looked for.

Hence communication with the microbiologist should be a standard clinical practice to ensure optimal identification of the microbes. Also, relevant information, like previous antibiotics used, co-morbid conditions and depth and extent of SSI should be provided to the microbiologist, thereby minimizing the chance of overlooking or missing the presence of atypical organisms. The microbiologist will then incubate the cultures for a longer period of 5 or more days and also by utilizing specific media (Table 5).

### Microbes which can be ‘missed’ on routine culture, but can cause SSI

There are many pathogenic microorganisms which cause SSI, but do not exhibit a positive growth on standard culture plates within 48 hours. Some examples are:

1. Atypical Mycobacteria
2. Mycoplasma and Ureaplasma
3. Legionella
4. “Small-colony variant” Staphylococcus aureus
5. Anaerobic pathogens

#### Atypical Mycobacteria:

These organisms grow more rapidly (compared to the typical mycobacteria species) within 5 days on standard blood agar plates. Common organisms are *Mycobacteria abscessus, M. chelonae* and *M. fortuitum*. Common clinical procedures where these organisms can cause postoperative infections are:

- Permanent cardiac pacemaker implantation.
- Laparoscopic procedures
- Breast operations

#### Mycoplasma and Ureaplasma

*Mycoplasma hominis* and *Ureaplasma urealyticum* are the common *Mycoplasmas* that can cause SSI. These are common in immunosuppressed patients. Commonest source is the persons own endogenous flora. These require special culture methods for optimum identification, as these are not included in routine culture protocols and must be requested by the surgeon, in all immunosuppressed patients with SSI. These are generally susceptible to tetracyclines and macrolides. Some of the common clinical procedures where these organisms can cause postoperative infections are:

- Cesarean section wounds
- Sternotomy wounds
- Vascular grafts
- Post-transplant surgery
- Orthopedic procedures
- Maxillofacial surgery

#### Legionella

Legionella species commonly cause lung infections. Rarely, they can gain access to surgical site by hematogenous route and result in SSI. They also spread by nosocomial route. They are thin gram-negative bacilli and are poorly visible on gram stain. They do not grow on ordinary culture media and need addition of special substances like cysteine and iron salts for optimal growth. Published case reports of SSIs caused by Legionella species include:

- Hemodialysis fistula
- Hip surgery wounds
- Sternotomy wounds

Legionella species are generally susceptible to fluoroquinolones or macrolides.

#### Small-colony variant-Staphylococcus aureus (SCV)

These species can be commonly mistaken for coagulase-negative staphylococci, as their coagulase test can be delayed. Also, they tend to grow rather slowly, and take more than 3 days to be identified (seen as small pinpoint colonies). Infection with these organisms tends to be less pathogenic, but they have the capacity to develop resistance to antibiotics, perhaps due to the fact that they persist intracellularly, and hence result in chronic infections.
A classic example is the persistent discharging infection, following a hernia repair with a synthetic mesh. They can also be the causative organisms of SSI in patients who received aminoglycosides as prophylactic antibiotic. These are generally susceptible to clindamycin and also medications that are effective against MRSA.

Anaerobic Bacteria:
The surgical site infections caused by these tend to be rare, but can result in a fulminant course. Common organisms are *Clostridium*, *Bacteroides* and *Prevotella* species. They cannot be cultured on routine aerobic media and need special anaerobic media. Appearance of dirty-water like exudates, which is culture negative, is a clue to the presence of these bacteria (*C. perfringens*). Infections caused by such organisms have a high mortality rate and debridement should be done early. They are susceptible to clindamycin and penicillins.

Organisms causing SSI which can be mistaken for contaminants
Coagulase-negative staphylococci (CNS) or even *Corynebacterium* species can cause postoperative wound infections, and yet diagnosed as ‘contaminants’! If these organisms are present in exudates at or more than $10^5$ colony-forming units/ml then they should be assumed as the cause of SSI. Some of the common clinical situations where these organisms cause SSI are:

i. Vascular grafts
ii. Prosthetic joints
iii. Prosthetic shunts
iv. Other implanted devices

Other assorted organisms causing SSI
These are comprised of a mixture of microorganisms can be difficult to culture and yet cause SSIs. They might need special culture media and PCR analysis to diagnose. They cause infections at various surgical sites. Some of these organisms are:

i. Actinomycyes
ii. Nocardia
iii. *Coxiella burnetti*
iv. *Gordona* species

Published literature on case reports include chronic sternal infections and mediastinitis following cardiac surgery, carotid artery rupture following resection of oropharyngeal carcinoma, facial infections following facial-cutaneous surgery.

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**Table 5: Duration and types of media used in Identification of microbes**

<table>
<thead>
<tr>
<th>Medium</th>
<th>Incubation Period</th>
<th>Microbes Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep blood agar</td>
<td>Aerobic for 3 days</td>
<td>Staphylococcus aureus and CNS</td>
</tr>
<tr>
<td>MacConkey agar</td>
<td>Deep tissues: 7 days</td>
<td>Streptococci, Enterococci, Gram –ve rods, Corynebacteria</td>
</tr>
<tr>
<td>Chocolate agar</td>
<td>Aerobic 4 – 7 days</td>
<td>Most RGM, Nocardia species</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCV Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional: Legionella and Mycoplasma</td>
</tr>
<tr>
<td>Buffered charcoal-yeast extract agar (BCYE)</td>
<td>Aerobic 4 -14 days</td>
<td>Legionella, Mycoplasma and Nocardia</td>
</tr>
<tr>
<td>CDC-anaerobic agar, CAN, LKV,</td>
<td>Anaerobic 14 – 28 days</td>
<td>RGM. Fungi, SCV Staphylococcus aureus</td>
</tr>
<tr>
<td>A7 &amp; A8 agar</td>
<td>Aerobic 3 – 4 days</td>
<td>Anaerobes, Nocardia species</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCV Staphylococcus aureus, Brucella,</td>
</tr>
<tr>
<td>Thiglycolate broth (Blood culture bottles)</td>
<td>Aerobic 7 – 14 days</td>
<td>Growth for all routine microbes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical remain alive for subculture</td>
</tr>
<tr>
<td>10B Arginine broth</td>
<td>Aerobic 3 – 4days</td>
<td>Special broth for recovery of Mycoplasma and Ureaplasma</td>
</tr>
<tr>
<td>7h9 broth with PANTATM</td>
<td>Aerobic up to 14 days</td>
<td>Antibiotic supplements broth for recovery of Mycobacterium species</td>
</tr>
</tbody>
</table>

RGM: Rapidly growing mycobacteria, SCV: Small colony variant
Role of clinician and microbiologist in management of culture negative SSIs

Managing SSI needs a close cooperation between the surgeon and microbiologist. The tenets of this clinical partnership can be summarized as follows:

i. Discuss with the microbiologist and provide all the clinical details, including the antibiotics in use (immediate past and present). The microbiologist in turn needs to do the following:
   a) Review the gram stain. This includes original smears as well as stains of broth into which the specimen has been inoculated.
   b) Review the original culture plate and hold it up to 2 weeks to allow growth of slow-growing microbes.
   c) Can subculture on specialized media.
   d) Request for a fresh specimen, which should be sent to laboratory immediately, which can then be cultured for acid-fast bacteria and fungus.

ii. Consider empiric therapy (after vigorous attempts have been made to identify the responsible pathogen in concurrence with the microbiologist) if SSI persists after routine treatment with first-line antibacterial drugs against common pathogens. The choice of antibiotics includes antistaphylococcal penicillins, cephalosporins, vancomycin, and β-lactum / β-lactumase inhibitor combination for suspected mixed infections.

iii. Consider additional diagnostic tests and special culture media and repeat cultures.

iv. Consider newer fluoroquinolones like levofloxacin on long course basis, as these are active against Mycoplasma, Legionella and other atypical mycobacteria.

Conclusion

Managing surgical site infections in the absence of positive culture can be difficult. In such situations, an effective communication with the microbiologist and infectious-disease specialist will enable a positive clinical outcome. The steps can be summarized as follows:

1) The standard plates to be incubated for an additional 5 to 7 days, which allows the ‘slow-growers’ to be identified.

2) Subculture the broth even in the absence of visible growth.

3) Repeat surgical biopsies if diagnosis is doubtful, with a request for special diagnostic studies.

Practice Points to Minimize Incidence of Culture Negative SSIs

i. Optimize preoperative morbidity.

ii. Ensure adequacy of operation theatre environment.

iii. Ensure adequate antisepsis at surgical sites.

iv. Ensure appropriate tissue handling.

v. Prevent breakdown of infection control procedures.

   a. Avoid rinsing instruments in contaminated surgical solutions, tap water or contaminated ‘sterile water’.

   b. Avoid contaminated gentian violet or methylene blue marking solutions.

vi. Institute appropriate evidence-based prophylactic antibiotics.

vii. Be aware of the recognized causes of culture negative SSIs.

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Further reading*


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