Complicated Skin and Skin Structure Infections (cSSSI’s): A Comprehensive Review

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Abstract Complicated skin and skin structure infections (cSSSI’s) are among the most common microbial infections occurring both in the community and the hospitals. Aetiology of cSSSI’s is complex and includes various microorganisms (bacteria, fungi, parasites and viruses). cSSSI’s in general are poly microbial in nature including both anaerobic and aerobic bacterial species. Primary cSSSI’s resulting from single bacterial species and secondary bacterial infections in patients suffering from skin conditions due to autoimmune conditions (eczema) or other microbial causes (viruses, fungi and parasites) have been reported in the literature. Occurrence of multi-drug resistant bacteria, underlying co-morbidities contribute to the complications in the management of cSSSI’s. Formulating effective guidelines for clinical, laboratory diagnosis, treatment and management of patients suffering from cSSSI’s would certainly be beneficial in the reduction of morbidity and mortality.

Keywords: complicated skin and skin structure infections (cSSSI’s), aetiology of cSSSI’s, multi-drug resistance

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1. Introduction

Complicated skin and skin structure infections (cSSSI’s) constitute microbial infections of skin and soft tissues. cSSSI’s may usually present as a mild superficial and suppurrative skin infection (pyoderma) and can later be developing in to severe necrotizing fasciitis involving subcutaneous connective tissues and spread deep in to other soft tissues [1]. cSSSI’s are a cause of huge public health problem resulting in both community acquired infections as well as nosocomial infections [2]. In the era of HIV and emergence of various infectious agents and malignancies, that may be responsible for compromised immune status of individuals, cSSSI’s can result in greater morbidity and mortality especially in the developing world. Prompt clinical and laboratory diagnosis and initiation of effective antimicrobial therapy remains mainstay in the management of cSSSI patients. Prevalence of multi drug resistance and associated co-morbidities including diabetes, chronic kidney diseases, liver dysfunction, cardiovascular diseases, viral infections (HIV, Hepatitis B virus, Hepatitis C virus and others), cancerous conditions and age of the patient influence the prognosis of cSSSI’s [3]. Studies have also noted that military personnel with war wounds are predisposed to cSSSI’s. The nature of infections in case of cSSSI’s has been confined to the area of inoculation and local spread to deep tissues, but dissemination hematogenously causing septicemia has also been reported [3]. Animal bite/scratch wounds may also be responsible for skin and skin structure infections (SSI’s) [4]. Predisposing factors that contribute to the development of cSSSI’s include peripheral vascular insufficiency, peripheral neuropathy secondary to diabetes/cardiovascular diseases, disrupted venous or lymphatic circulatory system, inoculation of foreign bodies (war wounds, accident trauma), poor hygiene and immunocompromised conditions (chronic renal failure, steroid use, immunosuppressive therapy, organ transplantation HIV infection) [5,6]. Classification of cSSSI’s is complex and depends on various clinical and laboratory parameters. cSSSI’s can be superficial, deep or disseminating hematogenously depending on the extent of invasion (superficial skin, sub cutis, fascia and muscle tissue). They can be either necrotizing or non-necrotizing and acute or chronic based on the presentation where acute infections usually take few days to weeks for resolving and chronic infections may take months to resolve. cSSSI’s can also be defined as those that require
2. Aetiology of Complicated Skin and Skin Structure Infections

In contrast to the other superficial skin infections the etiology of cSSSI’s usually is polymicrobial in nature including anaerobic bacteria. Potential causes for community acquired cSSSI’s include Staphylococcus aureus, group A Streptococci. Gram negative bacterial causes include non-fermenters like Pseudomonas aeruginosa, Acinetobacter spp and others, which are usually associated with nosocomial CSSI’s [5]. Ellie J C Goldstein et al in their study have revealed that 33.5% of cSSSI’s were polymicrobial in nature with abscesses, diabetic foot ulcer and post traumatic wound ulcers accounting for most of the cSSSI’s. The same study has shown that gram positive bacteria including Staphylococcus aureus were responsible for 24% of infections and 53% of cSSSI’s were attributed to gram negative bacteria including the anaerobes (Bacteroides fragilis, Prevotella spp, Pophyromonas spp, Fusobacterium spp, Veillonella spp and others. Among the anaerobic bacterial causes, 34.9% of the cSSSI’s were showing Peptostreptococcus spp [17]. Recent studies have also noted the occurrence of monomicrobial skin and skin structure infections (SSSI’s) involving Acinetobacter baumannii [18]. The same study has elaborated on the possible co-morbidities including severe physical trauma and liver cirrhosis, chronic kidney disease, obesity, old age and nosocomial infection associated with another pathogen, diabetes and cancer, which may complicate the management of SSSI’s [18]. It has also been noted that enterobacteriaceae members including Escherechia coli, Klebsiella pneumoniae and other bacterial species of gastrointestinal origin like Enterococcus faecalis may be responsible for both complicated and uncomplicated SSSI’s [6]. Other bacteria that have been associated with cSSSI’s include Vibrio vulnificus, Aeromonas hydrophila, Clostridium spp and group B, C, G Strplococcus spp and other microaerophilic bacterial species. Haemophilus influenza, Bacillus anthracis, pastuerella multocida, Pasteurella spp, Erysipelothrix rhsiopathiae and other vibrio spp including Vibrio carchariae, Vibrio damsela, Vibrio hollisae and vibrio alginolyticus have been noted causes of cSSSI’s Table 1 [4,6]. A recent study from Spain by Raya-Cruz M et al have evaluated skin and soft tissue infections in hospitalized patients and found that 66.7% infected patients presented with cellulitis/erysipelas and diabetes (33%), heart failure (17.7%) were found to be frequent co-morbidities. The same study has revealed that Staphylococcus aureus (35.1%) and MRSA(12.9%) were most common causes [19]. A recent study from India by Phakade RS et al has revealed that Staphylococcus aureus (73%) and streptococcus spp (12%) were frequent Gram positive causes for community acquired skin and soft tissue infections where as Pseudomonas aeruginosa (28%) and Acinetobacter spp (18%) were associated with hospital acquired SSI’s [20]. Skin, being the largest organ of the body present outside as a protection to the internal organs is most prone to external injuries. Skin and its underlying fatty layer, fascia, muscle is a tough and flexible structure that may be prone to infection/inflammation. Skin infections are best described way back in 1st century as calor, rubor, tumor, dolor, and fluor indicating heat, redness, swelling, pain and discharge respectively [3,21]. Skin consists of normal microbial flora including gram positive cocci, yeasts and other bacterial species, which protect it from invasion of potential pathogens. Trauma and breakage in this stricture may predispose the skin to have given access to colonization and invasion of pathogenic microorganisms.
### Table 1. Aetiology and predisposing factors contributing to complicated skin and skin structure infections (cSSSI’s)

| Aetiology | Predisposing factors |
|-----------|----------------------|
| **Common Bacterial causes** |  |
| Staphylococcus aureus | Diabetes |
| Coagulase negative Staphylococci (CONS) | Long term Steroid therapy |
| Streptococcus pyogenes | Neutropenia |
| Streptococcus spp (Group B, C, G and H) | Liver cirrhosis |
| Enterococcus spp | Burns |
| Pseudomonas spp | Alcoholism |
| Acinetobacter spp | Organ transplantation |
| Citrobacter spp | Malnutrition |
| Enterobacteriaceae members (Escherechia coli, Klebsiella spp, Proteus spp, Enterobacter spp, Serretia spp, Salmonella spp and others) | Infectious disease (HIV and others) |
| Vibrio spp | Extremes of age |
| Aeromonas hydrophila | Long duration hospitalization |
| Mycobacterium spp | Autoimmune diseases |
| Clostridium spp |  |
| *Haemophilus influenzae* |  |
| **Human and Animal bite/contact/ wounds** |  |
| Pasteurella multocida |  |
| Pasteurella spp |  |
| Campylobacter spp |  |
| Capnocytophaga canimorsus |  |
| Streptobacillus moniliformis |  |
| Bartonella henselae |  |
| Fransisella tularensis |  |
| Bacillus anthracis |  |
| Yersinia pestis |  |
| Spirillum minor |  |
| CDC group EF4 |  |
| Vibrio carhariace |  |
| Fusobacterium spp |  |
| Prevotella spp |  |
| **Unusual bacterial causes** |  |
| Vibrio flavidus |  |
| Vibrio vulnificus |  |
| Eikenella corrodens |  |
| Nocardia spp (soil contamination) |  |
| Erysipelothrix rhusiopathiae |  |
| Helicobacter cinaedi |  |
| **Infectious diseases presenting as Skin lesions** |  |
| Neisseria meningitidis |  |
| Streptococcus pyogenes (scarlet fever) |  |
| Rickettsial infections |  |
| Treponema pallidum (syphilis) |  |
| Candida spp (Tinea) |  |
| Crotococcus spp (Cutaneous) |  |
| Systemic fungal diseases |  |
| Angulostoma duodenale (cutaneous larva migrans) |  |
| Leishmania spp |  |
| Trypanosoma spp |  |
| Measles |  |
| Varicella zoster virus |  |
| Herpes virus |  |
| Human Immunodeficiency Virus |  |

3. Antimicrobial Therapy and Newer Therapeutic Approaches in cSSSI’s

Complicated SSSI’s are among the most common infectious conditions in human that warrant antimicrobial therapy. As most cSSSI’s involve more than one type of bacteria including the anaerobic bacterial species, choice of antimicrobials selected as empirical therapy must be having broad spectrum of activity. Empirical therapy should be formulated keeping in mind the frequency of multi-drug resistant bacteria, the beta-lactamase, Extended spectrum beta-lactamase (ESBL) and cabapenemase/metallo-beta-lactamase (MBL) producing bacterial species. A previous study that included patients suffering from cSSSI’s has noted that etrapenem and piperacillin-tazobactum were effective against more than 97% of bacterial species (anaerobic and aerobic bacteria) [17]. Having noted the frequent occurrence of MRSA and other multi-drug resistant gram positive bacteria, a study noted that telavancin, a newer injectible drug, a lipoglycopeptide having bactericidal activity was found effective against MRSA, vancomycin intermediate susceptible and vancomycin resistant gram positive bacterial isolates [22]. Another recent study that has evaluated the efficacy of telavancin and vancomycin against gram positive bacterial isolates of cSSSI’s has revealed that telavancin was indeed more effective (93%) than vancomycin (90%) against Panton-Valentine leucocidin (PVL) positive MRSA isolates [23]. In the era of multi-drug resistance, there is an argument on the cautious use of antimicrobial agents to reduce the possibility of development of resistance [24]. A study that has reviewed a decade long data on the incidences of cSSSI’s , the nature of therapy and the outcome of treatment has shown that the average cure rate among those who were not given antimicrobial therapy was 66%
as compared to those who were administered systemic antibiotics that included sulfonamides (91%) and penicillin (98%) group drugs [25]. Previous studies have also noted that topical antimicrobial therapy was not as effective as intravenous penicillin/sulfonamide therapy in the treatment of cSSSI’s [26]. Having noted the prevalence of multi-drug resistant gram positive bacterial involvement in cSSSI’s, a previous study has revealed the efficacy of daptomycin, a cyclic lipopeptide antimicrobial agent against vancomycin intermediate susceptible/ resistant, methicillin resistant and MDR strains of Enterococcus spp and Staphylococcus spp [27]. Comparative efficacy of newer and injectable streptogramin antimicrobial agent, the Quinupristin/dalfopristin (synercid) against conventional therapeutic agents (cefazolin, oxacillin, vancomycin) revealed that with regards to the clinical success rate both therapeutic strategies showed similar results. This study has also noted that bacteriological eradication rates were lower in Quinupristin/dalfopristin group (68%) than in conventional group (76%) and that drug related toxicity was higher in Quinupristin/dalfopristin group (66%) when compared with conventional group (28%) [28]. Activity of a newer cephalosporin, ceftaroline against both multidrug resistant gram positive bacteria and gram negative bacteria in cSSSI’s has been emphasized in a recent papers [29,30]. Novel antimicrobial combination therapy using colistin-rifampicin and carbapenem-sulbactum group have been found effective in the treatment of MDR strains of Acinetobacter baumannii [31,32]. A review article published recently has illustrated the activity (bactericidal/bacteriostatic) of preferred antimicrobial agents (linazolid, tigecycline, daptomycin, vancomycin, TMP-SMX, rifampicin, fosfomycin, clindamycin and quinupristin/dalfopristin) in the treatment of cSSSI’s and revealed that eradicate rate was highest (85%) among those treated with intravenous/oral linazolid [33,34]. Meta-analysis study performed on the efficacy of tigecycline in the treatment of cSSSI’s and other infectious diseases has revealed that tigecycline was not inferior (though some adverse drug reactions were noted) to vancomycin and other conventional therapeutic modalities in the management of cSSSI’s [35]. Efficacy of tigecycline in the treatment of complicated infections in hospitalized patients was evaluated in a prospective, multicenter and non-intervention study by Marcus J Zervas et al and found that clinical cure rate for the treatment of cSSSI’s was found to be 82%. Results from a recent randomized clinical trial has revealed that treatment with intravenous/oral moxifloxacin followed by oral amoxicillin-clavulanic acid was found both clinically and bacteriologically as effective as intravenous piperacillin-tazobactum in the treatment of cSSSI’s [36]. Monotherapy with moxifloxacin (oral/Intravenous) was found to be very effective and safe in the improvement and resolution of cSSI’s in a recent observational study [37]. A recent study from America has reviewed novel therapies for the treatment and management of skin infections caused by Actinobacter baumannii [38]. This paper suggested that being an opportunistic bacteria that is prevalent in the hospitals and having developed resistance to multiple drugs including production of the ESBL’s and MBL’s, therapeutic approach for the treatment of skin infections caused by A baumannii and other multi-drug resistant bacteria include bactericidal gene transfer therapy (introduction of plasmid containing bactericidal genes in to the pathogenic bacteria), bioengineering human skin tissue (human skin is bioengineered to produce non-tumorgenic, pathogen free human keratinocyte progenitor cells (NKS) capable of synthesizing host defence peptides such as cathedcins and defensins that help in wound healing), Nitic-oxide releasing nanoparticles (nano-technology mediated delivery of nitic-oxide nanoparticles in to the affected/infected skin is used to enhance wound healing), phage therapy (multi-drug resistant bacteria are cytolyased by infecting them with specific bacteriophages), photodynamic therapy (PDT) (use of non-toxic photosensitizers (PS’s) and harmless visible light, that in the presence of oxygen, generate reactive oxygen species that eliminate cancerous cells and kill infectious microorganisms) and radio immunotherapy (RIT) (a method where in the affected organ is exposed to radioactive material that is toxic and cytolytic in nature) [39-48]. Another approach to the treatment and management of complicated cSSI’s with MDR bacteria is named as unconventional therapy, where the antimicrobial agent is given in combination with a plant extract that act synergistically in the elimination of infection [49]. Utility of blue light (light wavelength of 415 ± 10 nm) as a therapeutic option for the elimination of skin infections caused by MRSA was studied in experimental mice by Tianhong Dai et al. This study showed that blue light was effective in rapidly reducing the burden of bacteria from the infection site [49]. Peptide antibiotics/anti infective agents which are considered as next generation therapeutic agents may help in the treatment and management of cSSI’s in future [51].

**4. Management of Complicated SSSI’s**

A recent study by Wilson et al, developed a severity-of-illness scoring system for the better management of cSSI’s based on the resultant clinical cure rates. This was later reviewed for its utility in scoring the disease and was found not suitable in predicting the clinical cure rate as these studies were not addressing the role of co-morbidities, epidemiological variability’s, demographical influences and clinical approaches [52,53]. In a recent retrospective observational cohort study by Garau et al that performed systematic analysis of data on management practices of cSSI’s collected from 129 centers in ten European countries, revealed that of the 1995 patients included in the study the mean age was 60 years . The study performed a review of disease characteristics, treatment modalities and clinical outcome. The results of the study revealed that 40% of the patients needed initial therapy change which was influenced by the co-morbidities (42.6%) and surgical procedure (44%). This study also showed that the mortality rate was found to be 3.4% and the mean hospital stay was 18± 19.9days [54]. Management of cSSI’s has been noted to be influenced by the nature of the clinical infection and its severity in to three classes (Class 1, Class 2, class 3, class 4). Classes 1 are all those patients with no systemic signs of toxicity and co-morbidities, class 2 patients include those who are systemically un well and have any one co-morbidity, class 3 includes patients who are clinically defined as showing
toxic signs and patients suffering from extensive necrotizing lesions are placed in class [4,55]. Previous studies have suggested that depending on the severity, cSSSI’s can be classified as un-complicated (impetigo, ecthyma, erysipelas, folliculitis, furunculosis and other superficial focal skin infections), complicated infections (secondary infections of diseased skin (autoimmune/infectious conditions), cellulitis, lymphangitis, carbuncles, traumatic, bite wounds and others) and soft tissue infections (peri-anal abscesses, diabetic wound infections, necrotizing soft tissue infections, Fournier’s gangrene, myonecrosis, clostridia/traumatic/attraumatic gas gangrene). Most SSSI’s are uncomplicated and require no hospital admission in contrast to the complicated SSSI’s that necessitate hospital stay and close monitoring. Management of cSSI’S require immediate attention on the extent of skin lesion (involving muscle/fascia), signs of toxemia, necessity for surgical intervention, diagnostic tests to be performed and the empirical antimicrobial therapeutic options [4,6,13]. After a thorough clinical evaluation and on making specific decision on the further management of patients either without surgical intervention (antimicrobial therapy-topical/intravenous) or having decided on surgical procedures (debridement/plastic surgery), the clinicians should consider laboratory evaluation for the possible aetiology and antimicrobial susceptibility patterns of the isolated infectious causes. Initiation of a broad spectrum antimicrobial empirical therapy (topical/systemic), or deciding on therapeutic options after the availability of antimicrobial susceptibility reports would be beneficial in better patient management of cSSI’S.

5. Conclusions and Future Perspectives

In the era of increasing antimicrobial resistance and occurrence of multi-drug resistant bacteria (MDR), studies have now been concentrating on the development of novel therapeutic peptide antimicrobial agents [56,57]. Patient management be made on careful clinical considerations, reducing the time to make a decision on how to manage (therapeutic only/need for surgical intervention), utilizing relevant and reliable laboratory diagnostic methods and initiating appropriate antimicrobial therapy [58]. Developing and poor third world nations will have to formulate effective management strategies for patients suffering from cSSI’S considering the fact that there is a huge cost of hospitalization and antimicrobial therapy associated with the treatment of cSSI’S.

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