Impact of Evolving Epidemiology on Treatments for Complicated Skin and Skin Structure Infections: The Surgical Perspective

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Skin and skin structure infections (SSSIs) comprise a diverse set of conditions encountered frequently in clinical practice. Their severity ranges from abscesses to severe necrotizing infections.[1] The majority of SSSIs are uncomplicated, including small abscesses, impetigo, furuncles, and non-necrotizing cellulitis.[1,2] Uncomplicated infections are superficial or self-limited and can be managed successfully with incision and drainage alone or in combination with oral antibiotic therapy.

Complicated SSSIs (cSSSIs), the focus of this review, tend to be severe, more difficult to treat, often require surgery, and may be both limb- and life-threatening.[2,3] The US Food and Drug Administration (FDA) description of cSSSIs includes deep or necrotizing infections that require surgical intervention, including infected ulcers or burns, major abscesses, extensive cellulitis, or infections of any severity in the setting of specific medical comorbidities (ie, diabetes mellitus, chronic kidney disease, peripheral arterial disease).[4] These infections often involve deep fascia and muscle.[5] In 2010, the FDA released new guidance for clinical trials of antimicrobial agents for the treatment of acute bacterial skin and skin structure infections (ABSSSIs), to define clearly how an antimicrobial agent should be evaluated for a skin infection indication.[6] The term ABSSSI includes extensive cellulitis/erysipelas, wound and surgical site infections (SSIs), and major cutaneous abscesses that have a minimum surface area (erythema, edema, or induration) of 75 cm^2. In general, ABSSSI describes a cohort of infections of lesser severity than does cSSSI (with some overlap). Additionally, FDA guidance for new clinical trials of antibiotics for skin infections suggests assessment of clinical outcomes at 48 to 72 hours after initiation of therapy.

The incidence of cSSSI has been increasing over time. From 1993 to 2005, the annual number of emergency department visits for management of cSSSI increased approximately 3-fold.[7] Hospital admission for cSSSI is also occurring more frequently. The number of patients with a primary diagnosis of skin and soft tissue infection (SSTI) who were admitted to the hospital increased by 29% between 2000 and 2004.[8]

Surgical site infection (SSI) is a specific type of skin structure infection that occurs at the site of an operative procedure within 30 days after operation (1 year after an implant).[9] Data from the US Centers for Disease Control and Prevention (CDC) indicate that 2.6% of operations performed in the US are associated with SSIs.[10] This may be an underestimate because infections in the ambulatory surgery population are difficult to define and are under-reported,[11] considering that as many as 50% of SSIs are not recognized until after patient discharge. Surgical site infections are categorized as superficial incisional, deep incisional, or organ/space. Superficial incisional SSIs involve the skin or subcutaneous tissue of the incision and lead rarely to systemic toxicity.[11,12] Deep incisional SSIs involve tissues down to and including fascia and muscle. Organ/space SSIs comprise a multitude of infections and involve any body cavity that was opened or manipulated during surgery. The deepest extent of infection is used for classification purposes.

Results of concerted efforts to reduce the incidence of SSI have been mixed. In 2006, the Surgical Care Improvement Project (SCIP) was developed by the Centers for Medicare and Medicaid Services (CMS), with a goal of reducing surgical complications by 25% by 2010.[13,14] Performance measures include timing and choice of antimicrobial prophylaxis, discontinuation of antimicrobial agent within 24 hours, proper hair removal, blood glucose control for cardiac surgery, and maintenance of normothermia in colorectal surgery patients.[13] Using SCIP, Hawn and colleagues[15] were unable to

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Abbreviations and Acronyms

ABSSSI = acute bacterial skin and skin structure infection
CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*
cSSSI = complicated skin and skin structure infection
MIC = minimum inhibitory concentration
MSSA = methicillin-susceptible *Staphylococcus aureus*
PVL = Panton-Valentine leucocidin
SCIP = Surgical Care Improvement Project
SSI = surgical site infection
SSTI = skin and soft tissue infection
VRE = vancomycin-resistant *Enterococcus*
VRSA = vancomycin-resistant *Staphylococcus aureus*

document an improvement in SSI rates, either at the patient level or in rates associated with the hospital. Many causes of SSIs may be unaccounted for, so the SCIP measures may be an oversimplification.[16] In addition, the performance measures of the project may be flawed by what is included. For instance, methods for surgical prophylaxis have been updated to provide a standardized approach so that in most circumstances, single-dose antimicrobial prophylaxis is appropriate.[17,18] However, SCIP recommends administration of antibiotic prophylaxis for longer than is usually necessary.[16]

Complicated SSSIs are associated with considerable cost, prolonged hospital stay, and increased mortality rates.[10,19] Hatoum and associates[20] compared the outcomes of patients with cSSSI to those of matched controls with similar comorbid diagnoses (apart from cSSSI). In a fixed-effect regression model, length of hospital stay and total hospital charges were 3.81 days longer and $14,794 greater for patients with cSSSI, respectively ($p < 0.0001$). In addition, mortality was increased in patients with cSSSI (5.4% vs 3.5% in patients without cSSSI; $p < 0.0001$). In a study of 255 patients with SSI, total attributable cost was nearly $2 million more than for matched uninfected patients.[10] Most published reports of the economic impact of SSI provide only hospital cost; nonhospital cost or cost for patients treated on an outpatient basis are often not included. Additionally, some operations after which SSI is common have not been evaluated in economic terms (eg, necrotizing abdominal wall infections, infected vascular prostheses); therefore, the true economic impact of SSI may be underestimated.

Encountered frequently by surgeons, cSSSIs can cause substantial morbidity and mortality. These infections can often be treated with surgical intervention, but appropriate antimicrobial therapy is necessary. This article discusses trends in causative pathogens and resistance, current treatment practices, and antimicrobial treatment options for cSSSI.

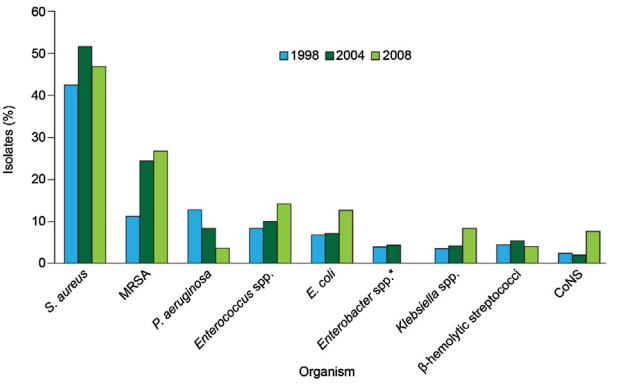

Figure 1. Frequency of pathogens isolated from cSSSI among hospitalized patients in surveillance studies, 1998 to 2008.[22-25] **Enterobacter* spp data not available for 2008. Note: MRSA is listed as a percent of total infections; these isolates are also contained within the *Staphylococcus aureus* percentage. CoNS, coagulase-negative staphylococci; cSSSI, complicated skin and skin structure infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

Trends in causative pathogens and microbial resistance

Complicated SSSIs are mediated predominantly by gram-positive pathogens, such as *Staphylococcus aureus* and *Streptococcus pyogenes*.[21] However, a diverse etiology is associated with cSSSI including gram-positive, gram-negative, and mixed infections (Fig. 1). The causative pathogen for cSSSI is dependent on a number of factors, including infection severity, microbial virulence, clinical setting, geographic location, initiating process, and host defenses. The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program, a study of cSSSI isolates from 27 US medical centers collected in 2008, reported *S aureus* (46.9%), *Enterococcus* spp (14.2%), and *Escherichia coli* (12.7%) as the most frequent bacteria isolated[22] (Table 1). Similarly, in 2012, the AWARE program evaluated isolates from 163 US medical centers and reported *S aureus* (55.5%), *E coli* (5.9%), and *Klebsiella* spp (5.5%) as the most frequent bacteria isolated.[23] Surveillance data from SSI demonstrate a shift toward gram-positive pathogens, with common causative pathogens being *S aureus* (33%), coagulase-negative staphylococci (CoNS) (11%), enterococci (8%), and *E coli* (6%).[24] Nevertheless, SSI can be influenced by several external factors and can be infected by normal exogenous gram-positive flora, endogenous enteric pathogens (eg, *faecalis* or Enterobacteriaceae), or nosocomial pathogens within an institution.[21]

Resistance to antibiotics is increasing among common cSSSI pathogens including *S aureus, S pyogenes, Enterococcus* spp, *Pseudomonas aeruginosa, E coli,* and *Klebsiella*