Clinical and microbiological profile of skin and soft tissue infections (SSTI) leading to sepsis

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Abstract

Preamble: Skin and soft tissue infections (SSTI) are an important cause of sepsis. Acute skin failure may result from many dermatological conditions. In this study we tried to highlight the role of skin failure as a component of multiple organ dysfunctions.

Materials and Methods: All adult patients (>18 years) diagnosed clinically as sepsis due to skin and soft tissue infections were included. Risk assessment was done using various parameters. Identification of pathogens and their antibiotic sensitivity pattern was performed by blood and skin swab cultures.

Results: A total of 55 patients (31 male and 24 female) were included in the study. The common causes of SSTI were surgical site infections, cellulites, necrotisingfasciitis, traumatic open wounds, Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, burns, bed-sores, unknown wounds and others. The major risk factors identified were the percentage of skin involvement, depth of wounds, presence of unhealthy granulation tissue and co morbidities like diabetes and immunodeficiency. MRSA and ESBL producing gram negative bacteria were important causative microbes for SSTI induced sepsis.

Conclusion: SSTI is one of the important causes of sepsis. Early recognition and management of risk factors can prevent adverse outcome. Knowing microbiological etiology and drug sensitivity pattern is important is connection with SSTI related sepsis. Septic shock was identified as most important organ failure on admission leading to death in patients having SSTI related sepsis.

Keywords: Skin and Soft tissue infections (SSTI), Multiple organ dysfunction syndrome, Risk factors, SCORTEN.

Introduction

Skin and soft tissue infection (SSTI) is an important cause of sepsis. It was ranked fifth important cause and was present in 11% of sepsis patients in four general, acute care hospitals of New York, United States.[1] It is one of the common condition observed in patients presenting to emergency departments and are sometimes severe enough to induce septic shock which requires admission in intensive care unit (ICU).[2] Sepsis may occur from skin and soft tissue infections as organisms may enter the body through breaks in the skin from the external environment and may enter the blood in susceptible individuals.

Sepsis may lead to mortality when host response to infection causes organ dysfunction which may be in the form of septic shock and multi-organ system failure. Presence of altered organ function in two or more organ systems having systemic inflammation or sepsis is termed as multiple organ dysfunction syndrome(MODS).[3] Skin as an organ or as a part of integumentary system, which may be the cause of sepsis and more importantly effect of sepsis is not studied by many.[4] Acute skin failure and dysfunctional skin may result from toxic epidermal necrolysis, erythroderma with subsequent scaling, denudations of bullous dermatoses and others which can be considered as a dermatological emergency.[5] Petechiae and purpura may be accompanied with systemic bacterial or viral infections or may be the effect of sepsis. Sepsis-associated purpura fulminans in adults is accompanied with septic shock, disseminated intravascular coagulation and circulatory failure leading to multiple organ dysfunction.[6]

Sepsis screening for acutely ill, high-risk patients is one of the important ethoses in sepsis survival campaign.[7] Recognition of high risk patients who are prone for sepsis by dermatological perspective is important, as skin is largest organ of the body. Appropriate education in regards to role of skin in sepsis prevention may help reducing the risk for sepsis.

Materials and Methods

Recognition of clinical/dermatological signs which can forecast severe infection and sepsis, identification of causative microbial agents and assessment of host risk factors as well as pattern of organ dysfunction was the aim of present study. This was an observational, cross sectional, clinico-microbiological study conducted from September 2012 to December 2016. After institutional ethical committee approval, this study was conducted at tertiary care hospital which caters services to rural as well as nearby urban patients. All adult patients above the age of 18 years diagnosed clinically as sepsis by 1992/2001 definition (Sepsis = Systemic inflammatory response syndrome (SIRS) criteria when two or more of the following were present: temperature > 100.4 ºF/38 ºC or < 96.8 ºF/36 ºC; heart rate > 90/min; respiratory rate > 20/min or

$PaCO_2$ < 32 mm Hg; and WBC count > 12,000/mm3, < 4,000 mm3, or > 10% immature forms) with skin and soft tissue infection as a cause of sepsis were included in this study. It included patients in whom skin and integumentary system was the causative factor for sepsis. These included skin and soft tissue infections like cellulitis, necrotising fasciitis, postoperative skin/suture infections, abscess, burns involving skin and soft tissue, traumatic wounds, diabetic foot ulcer, carbuncle, pressure sore and decubitus ulcer, drug reactions, gangrene and other conditions which affected skin and skin structure and no other causes of infection (other than skin and soft tissue) were identified. Risk factor appraisal was done which included various parameters of which skin surface area was assessed by using Wallace "rule of nine".[9] Another indicator for risk assessment was depth of the wound which was judged by NPUAP staging.[10] All these patients were admitted in critical care wards. Cultures of different samples including blood were done for identification of the possible bacterial and fungal pathogens. Markers of sepsis like CRP and PCT were also done. Organ involvement in sepsis was detected by clinical as well laboratory criteria which is included in MODS and SOFA score.[11]

Results

55 patients developed sepsis due to skin and soft tissue infections, of which 31 (56.36%) were male and 24 (43.64%) were female patients. 06 (Male 01+Female 05) were in 18-30 age group,12(M 08+F 04) in 31-40, 10(M 07+F 03) in 41-50,15(9+6) in 51-60,10 (4+6) in 61-70 age group and 02 male patients were above age of 70 years. Mean age of male patients was 50.22, of female was 46.42 and average age of all patients who developed sepsis due to SSTI was 48.49. Of 55 patients, 14 patients expired in the hospital; while two patient's condition was bad and thus they were taken home against medical advice (DAMA). Thus adverse outcome was present in 16 patients while 39(70.90%) patients survived (Table 1).

Skin and soft tissue infections like cellulitis and necrotising fasciitis (NF) was the cause of sepsis in 12 (21.82%) and 3(5.45%) patients respectively, of which 5 patients of cellulites and 1 patient of NF died. Traumatic wound, majority due to road traffic accident lead to sepsis in 9 patients of which one patient died. One of these who was diabetic developed sepsis due to bad multiple wounds caused by dog-bite. 4 patients, three female and one male had burns and all 4 died due to sepsis related MODS. Surgical site infection in form of incisional skin and soft tissue infection lead to sepsis in 16 patients. Diabetes was present in 6 of 16 (37.50%) patients.14 patients survived while 2 had adverse outcome in form of hospital death in 1 and other one was a DAMA subject, whose condition was bad on egress. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) with sepsis was present in 2 male patients and one male patient had acute generalized exanthematous pustulosis (AGEP) with MODS related to sepsis (Fig. 1 and 2). One elderly female patient of hemiplegia had bed-sore related sepsis and was admitted in ICU for the same. In four patients, open wound was present which was infected and specific history of trauma or burns was not available. History of application of some indigenous herbs to the skin was available in these patients. Three patients had miscellaneous cause of skin related sepsis. First one had metastatic cancer who developed lymph edema and local chemotherapy port-site infection and sepsis. Second patient had SLE, traumatic wound and was on corticosteroids therapy died due to sepsis. Third patient in this miscellaneous study group had temporary skin rash (Dengue serology negative) with septic shock and MODS due to probably viral sepsis, died in the hospital (Table 1).

For clinical profile, skin findings and risk assessment of patients having sepsis, eight criteria was taken which included (I) Skin area involved, (II) Depth of the involvement of skin/soft tissue, (III) Wound inspection findings, (IV) Associated presence of Diabetes, (V) Immunodeficiency (other than Diabetes), (VI) Age≥60 years, and (VII) Increased procalcitonin (PCT) levels. Results of these 07 criteria are recorded in table 2. Clinical findings were related to adverse outcome of the patients like death, MODS and bad prognosis at discharge. Local site observation of skin and soft tissue was the eighth criterion which was done as a qualitative data. Increased local temperature, unhealthy granulation tissue, intense erythema progressing to dusky discoloration, pain and local tenderness, swelling and induration were present in these patients. There were 2 patients having orbital cellulites who had poor outcome.

Blood culture and pus/skin swab culture was done in all patients. Total 66 specimens were obtained as skin-swab, pus or wound drainage fluid. Culture was obtained from single specimen in 47 patients, from 2 specimens in 6 patients, 3 specimens form one and 4 specimens from 1 patient. Total 59 blood cultures were done from 55 patients. It was done once in 52, twice in 02 patients and thrice in 01 patient. Results of blood and local site/ pus/ wound drain culture are depicted in table 3. Data analysis of culture results were done in regards to a case and not as isolates and first positive result of organism is captured in the table 3. In these patients, specimens like urine, ET tip, sputum and other body fluid culture was done in 9 instances which had yielded no growth in 2 and other 7 it was associated catheter induced secondary infection in 5 and ventilator associated pneumonia in 2. We did not do culture for anaerobes.

Staphylococcus aureus was the commonest organism isolated. Other gram positive organisms were *Coagulase-negative Staphylococcus (CoNS), Enterococcus species* and *Streptococcus pyogens*.

(Table 3) All *Staphylococcus aureus* isolates were Methicillin resistant while sensitive to vancomycin as well as Linezolid (95%). High percentage of resistance was seen against penicillin (98%) and erythromycin (68% to 100%). Intermediate degree of resistance pattern was obtained in descending order with Ciprofloxacin, Gentimicin, Levofloxacin and Doxacycline. *Klebsiella* species, *Escherichia coli*, *Acenatobacter* spp, and *Pseudomonas aeruginosa* were common gram negative organisms isolated as shown in table 3. Least resistance was noted against imipenem/ertapenem/meropenem while about three fourth of these gram negative organisms were resistant to Cefuroxime, Cefotaxime, Ceftazidime and Ciprofloxacin. Four patients of burns had sepsis due to P*seudomonas* spp. showed high degree of resistance to almost all antibiotics and showed intermediate degree (50% isolates) of resistance to imipenem and etrapenam/meropenem.

Of 55 patients with SSTIs, 31 had no organ dysfunction on admission but had SIRS criteria with evidence of sepsis. Majority (29 of 31) of such patients survived and 2 of them developed severe sepsis and died. Three patients had single organ involvement of which 2 had acute kidney injury and 1 had acute lung injury. Giving organ support with treatment of infection, 2 patients survived. MODS on admission was present in 21 patients of which 11 patients died and 2 patients were bad on egress.8 patients survived who had MODS on admission. Of 6 patients who had septic shock associated with MODS had adverse outcome. Common organ involvement on admission was kidney, lung, brain, blood, liver in decreasing order of frequency. Thrombocytopenia was present in 4 patients on admission as a part of multiorgan failure. Supporting lung and kidney helped in survival of sepsis patients. Hypothermia was present in 2 patients on admission which lead to adverse outcome in both. (Table 4)

Table 1: Skin and soft tissue infections leading to sepsis

S. No.	Condition	No.	Male	Female	S/D/DAMA[#]	Diabetes as co morbidity
1	Cellulitis	12	7	5	7/5/0	6
2	Necrotising fasciitis	3	3	0	2/1/0	0
3	Traumatic open wound	9*	6	3	7/1/1	1
4	Burns	4	1	3	0/4/0	0
5	Surgical site infection	16	6	10	14/1/1	6
6	SJS/TEN	2	2	0	2/0/0	0
7	AGEP	1	1	0	1/0/0	0
8	Bed sores	1	0	1	1/0/0	0
9	Unknown wound	4	3	1	4/0/0	0
10	Miscellaneous	3	2	1	1/2/0	0
	Total	55	31	24	39/14/2	13

[#] S-Survival D-Death, DAMA-Discharge against medical advice

Table 2: Skin/soft tissue findings and risk factor analysis:

S. No.	Risk factor	Risk factors present in	Condition in which it was present	Relation with adverse outcome
1.	Skin area involved	10	Cellulites (2) SJS/TEN (2) Burns (4) AGEP (1) temporary rash and septic shock (1)	Of these 10 patients, 07 died.
2.	Stage 3 and 4: deep involvement of skin/soft tissue	5	Bed-Sore patient (1) traumatic wound (4)	One patient expired
3.	Wound observation	29(16 incision wound,4 unknown aetiology wound and 9 traumatic wound)	Yellow pus discharge with unhealthy granulation tissue with slough in majority of wounds.	Of 29 wounds related sepsis, 2 patients died and 2 had DAMA status
4.	Associated Diabetes	13	Present in 6 patients of cellulites and 6 patients of SSI and 1 patient of Dog-bite	2 patients died who had cellulites and diabetic foot.

5.	Immunodeficiency other than Diabetes	04	Patients were on Corticosteroids (02),) on cancer chemotherapy(1), Huge Splenomegaly (1)	A patient had SLE & open wound and second one had huge splenomegaly with orbital cellulites. Both died.
6	Age≥60 years	16	16 patients	5 died.
7	Moderate to high increased in Procalcitonin≥2.0 ng/ml	Was possible in 10	8 (Raised in all 10 which was >0.5).	3 died. Procalcitonin was 10, 2.4 and 2.5.

Table 3: Microbiological profile of skin and soft tissue infections (SSTI) leading to sepsis

S. No.	Micro-organism/growth	Blood Culture*	Pus/skin lesion Culture*
1	*Staphylococcus aureus*	09	10
2	*Klebsiella* species	08	09
3	*Escherichia coli*	07	07
4	*Acenatobacter* spp.	06	03
5	*Pseudomonas aeruginosa*	04	05
6	Coagulase-negative *Staphylococcus*(CONS)	04	03
7	*Candida* spp	02	01
8	*Enterococcus* species	01	02
9	*Citrobacter* spp.	01	01
10	Unidentified gram negative bacilli	01	00
11	*Streptococcus pyogenes*	01	02
12	No growth	11	12
	Total	55	55

First positive culture result is tabulated in patients in whom multiple times samples were obtained.

Table 4: Organ dysfunction pattern on admission and their relation to outcome

S. No.		No of Patients	Adverse Outcome(n=16)	Survived Patients (n=39)
1	Sepsis without organ involvement	31	02	29
2	One organ Involvement	03	01	02
3	Multi organ involvement without septic shock	15	07	08
4	MODS with septic shock	06	06	00
	Total	55	16	39

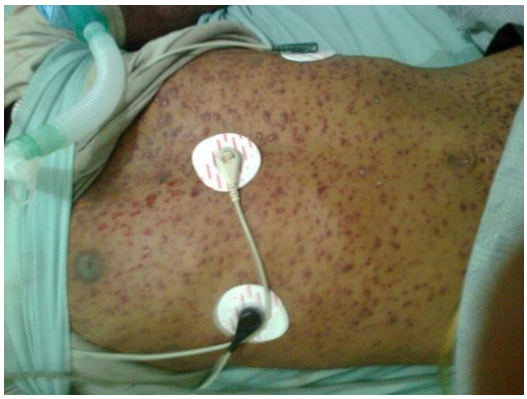

Fig. 1: Photo showing patient of AGEP, having 70% skin surface area involved with MODS. Patient on Ventilator

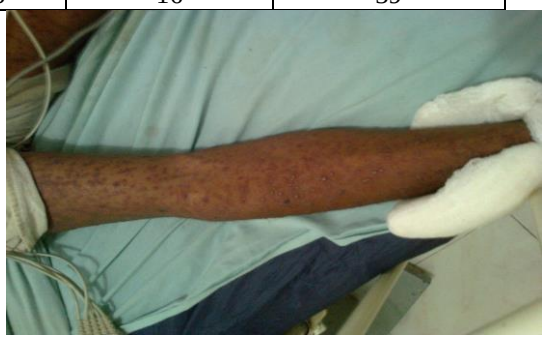

Fig. 2: Photo of same patient of AGEP having lower limb involvement

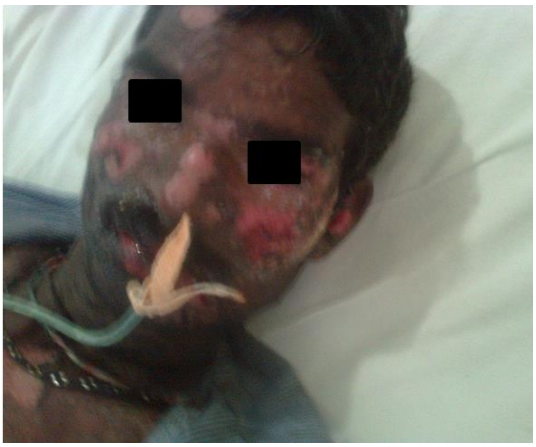

Fig. 3: Photo of patient having TEN showing multiple superficial erosions over face with involvement of oral and conjunctiva mucosa

Discussion

Skin and Soft Tissue Infection (SSTI) is one of the common causes for visits by patients to physician office, hospital outpatient and emergency department.[12] A problem known to cause death, if not diagnosed and treated early, is being recognized since ancient times which is further evolved as a challenge in modern times because of antibiotic resistance menace.[13] It is one of the treatable and preventable causes of sepsis. Severe skin and soft tissue infections being common at our tertiary care, rural based medical college attached hospital; we planned this study to get more dermatological insight. It was also aimed to study profile of SSTIs related sepsis occurring in less privileged populations to whom our institution is catering to. There were some meaningful observations of or study group patients having SSTIs related sepsis like neglected skin lesions for long time and in addition applying unscientific, indigenous herbs, poor diabetic control, sepsis due to wounds caused by dog-bite in diabetic patient, neglected pressure sore, not recognizing devitalized skin and infected wound, overuse of local and systemic corticosteroids, getting burns while cooking and others. There were 4 patients in this study who had infected wound and they were not able to give history related to cause of wound.

Skin, an important big organ having multiple functions is not been given due importance by acute care physician. Role of skin as first line defense and organ playing role in immune protection though well described is not integrated with acute critical conditions except acute drug reactions. In our study selection of patients were based on broader skin conditions which are not routinely seen by dermatologists like burns and surgical site infections. This is to study the common denominator, which is skin wherein their distinctive functions are affected. Other conditions which were included was Skin and soft tissue infections like cellulites, Necrotising fasciitis, Traumatic wound, Stevens–Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP),bed sore and others.

In this study, there was male preponderance. Of 55 patients, 31 (56.36%) were male and 24 (43.64%) were females. Male preponderance may be due to more incidence of traumatic injury due to their occupation and greater exposure to driving. 4 patients were of 60 years, 10 were in 51-60 group and 02 patients were above age of 70 years. Out of total 16 patients, 5(31.25%) patients died. Mean age of sepsis in study patients was 48.49. It reflects two facts, one that it was middle aged group and younger patients which were affected and prevention of this will save active fruitful lives. Second fact is that age was not a very important risk factor, as out of adverse outcome in 16 patients only 5(31.25%) were of the age 60 and above. Again same numbers of patients (16 of 55) were elderly (≥60) which means 68.75% were below 60 years. Though some prognostic scores which is used to predict prognosis of critically ill patients does include "Age" as a parameter like APACHE (Acute Physiology and Chronic Health Evaluation),CURBS-65 for pneumonia patients and PREDICT (predicted Risk, Existing Diseases, and Intensive Care Therapy) model, the score which is specific for sepsis like SOFA does not include "Age" in risk calculation.[14] In this study also age does not seem to be very important prognostic marker, however large population multicentric study related with "AGE" as independent variable to generate valid evidence.

We tried to find the risk factors for sepsis in patients with skin and soft tissue infections. We had chosen eight important clinical findings which we thought worth recording and these findings were related to genesis of sepsis, organ dysfunction and adverse outcome. It was observed that greater than 10% skin surface area was involved in ten patients out of 55, of which 7 patients died. (70%) Apart from skin surface area, initial epidermal detachment also is an important prognostic factor as described in "severity-of-illness score for toxic epidermal necrolysis (SCORTEN)".[15] Patient having AGEP had extensive skin involvement of 70% and MODS, but as epidermal barrier was not breached in this patient, he recovered. Another risk factor we studied was depth of the wound judged by Grade 3 and 4 by NPUAP staging.[5] patients had deep wounds of grade 3 and 4 with MODS of which one died. This fact helps us correlate that the dermis also plays an important role as a barrier organ. Most of the patients in our study that ultimately progressed to sepsis and MODS had wounds with unhealthy granulation tissue. Unhealthy granulation tissue is dark red in colour, contains yellowish exudates and bleeds on touch.[16] Presence of associated diabetes was an important finding in patients with skin and soft tissue infections leading to sepsis.[6] patients of cellulitis, 6 patients with surgical site infections and 1 patient of dog bite had associated diabetes. In a study done by

Hirsch et al, diabetic patients showed greater predisposition to wound infection as compared to non diabetic patients.[17] Delayed wound healing and vascular dysregulation which predisposes to infections may be the cause in diabetic patients. Other immunodeficiency states like patients on corticosteroids, cancer chemotherapy and pancytopenia due to splenomegaly led to severe wound infections in 4 patients in total. The patients who had massive splenomegaly also developed orbital cellulitis while another patient on long term corticosteroids for Systemic Lupus Erythematosus succumbed to sepsis following a wound infection. Procalcitonin was an important marker of sepsis and was elevated in all 10 patients in whom it was performed. Out of these 10 patients 3 patients died.

Here we would wish to highlight two cases, one of acute generalised exanthematous pustulosis (AGEP) who had MODS but survived and second case of generalized temporary rash in patient who died due to septic shock. Patient of AGEP had sterile pustules as reported in literature but Blood culture from this patient was positive for *Klebsiella* organisms.[18] Patient was HIV negative and had no other premorbid immunodeficiency. His PCT level was high. He had 70% skin involved with skin continuity normal. Postulation made in this case was that immune functions of skin were affected in this patient and this may be the reason for gram negative septicemia with MODS. (Fig. 1 & 2) This could be due to the fact that the epidermal barrier was not breached. Another patient who presented to us as viral sepsis with MODS and septic shock syndrome had temporary rash involving 80% of surface area. Dengue serology was negative. He died within two days of hospital stay. These patients who had extensive skin involvement without loss of skin continuity and still developing sepsis was to stress on powerful "Skin –Immune System (SIS)" which works as innate and adaptive immune system related to humoral as well as cell mediated immunity.[19]

Susceptibility and resistance pattern of antimicrobials agents against microbes causing SSTI has played an important milestone in history of medicine.[20] Methicillin-resistant S. aureus (MRSA) was commonest organism isolated from the skin and blood in this study. It was cause of one sixth of our patients who developed sepsis. Most MRSA isolates were sensitive to vancomycin and linezolid. MRSA infections is commonly found which was infections among patients in the emergency department.[21] Previous colonization and low socioeconomic status is a feature identified related to MRSA organism.[22] *Streptococcus pyogenes* was isolated in 2 patients having Necrotizing fasciitis patients were treated with broad spectral antibiotic as was assumed to be polymicrobial but after report treated with clindamycin and surgical debridement and 2 of our patients recovered while one died. Anaerobes could cause NF, however we were unable to culture them. This may be one limitation of this study. ESBL producing Gram negative organisms were also cause of sepsis. It is reported in literature that Gram negative organisms is cause of sepsis if SSTI is in lower extremity, abdominal and perineal region.[22] Systematic review of historical literature done by Spellberg B et al had shown that Penicillin was effective in curing complicated Skin and skin structure infection in around 98% cases which is now almost ineffective in majority of our microbial isolates found in sepsis patients.[23]

Organ dysfunction is considered to be very important component of sepsis and outcome and bearings will depend on type of organ dysfunction on admission.[24] Sequential assessment with SOFA score may help to know prognosis.[25] Of 55 patients 21 developed MODS, of which 13 patients had adverse outcome of which 6 had septic shock. We observed septic shock on admission as very important risk factor for adverse outcome. We postulate that skin as an organ has relation with septic shock. It is because skin has large vascular bed underneath, which when affected leads to adverse outcome.

Conclusion

SSTI is one of the important causes of sepsis. Early recognition and management of risk factors can prevent adverse outcome. Knowing microbiological etiology and drug sensitivity pattern is important is connection with SSTI related sepsis. Septic shock was identified as most important organ failure on admission leading to death in patients having SSTI related sepsis.

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