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Age and Infection: A Comprehensive Study of Synergistic Gangrene

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ABSTRACT

Objective: To analyze and interpret the impact of age on the etiology of synergistic gangrene, identifying key age-related risk factors, bacterial profiles, clinical presentations, and treatment outcomes.

Study Design: Retrospective cross-sectional.

Place and Duration of Study: Sheikh Zayed Hospital, Rahim Yar Khan and Combined Military Hospital, Bahawalpur Pakistan from Aug 2019 to Aug 2023.

Methodology: 288 patients were included. Patients with incomplete data or follow-up were excluded. Data collected for demographic details, clinical information, laboratory findings, and treatment modalities. Data analysis done and chi-square test applied. Patients divided into age groups: 18-30, 31-60, and over 60 years.

Results: Young and middle-aged patients have moderate disease of limb (30%) and abdomen (51%) respectively, compared to old patient having severe disease involving perineum predominantly. Diabetes mellitus and hypertension were present among all groups with statistical significance (p<0.02 and 0.07 respectively). The leukocyte count was reflective of severe infection in old group (16.2±3.03 x 10^9/L) compared to moderate disease in young (14.4±2.51 x 10^9/L) and middle age (10.8±2.03 x 10^9/L). The bacterial isolates show polymicrobial infections in young age, streptococcus pyogenes (27%) and E.coli (19%) in middle age, and streptococcus in older age group (35%). The mortality rate was 17%.

Conclusion: Synergistic gangrene affects all age groups with male predominance with variable intensity. The younger and middle-aged males have moderate disease predominantly of limbs and abdomen respectively contrarily to older age group having severe disease with perineal involvement. Diabetes mellitus and Hypertension were prevalent among all groups. The bacterial profiles vary by age from polymicrobial (young) to streptococcus and clostridia (old).

Keywords: Age, Bacterial Isolates, Immune Response, Necrotizing Fasciitis, Synergistic Gangrene.

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INTRODUCTION

Synergistic gangrene, also known as necrotizing fasciitis, is a life-threatening soft tissue infection that can progress rapidly presenting a daunting challenge to the attending physician across the world.[1,2] It is a dangerous bacterial infection that affects deep layers of the skin and soft tissues resulting in tissue necrosis, systemic problems, and even death. It continues to put medical professionals to the test for its queer onset, complex microbial relationships, and rapid deterioration.[3]

A lot of scientific work on synergistic gangrene is already present in the literature focusing on its overall risk factors, clinical manifestations, and treatment options.[4,5] Still, a notable research gap exists regarding its potentially varied etiology in different age groups. The exact mechanism by which age influences the development of synergistic gangrene and its progression is mostly unexplored, leaving our understanding of the subject lagging behind. This in turn results in a lack of specific investigations that determine the interaction of age-related physiological, immunological, and behavioral factors in the development, severity, and outcomes of synergistic gangrene.[6] This research gap needs to be addressed by extensive research for devising specific investigations, improving diagnostic approaches, and refining treatment protocols for age-specific cohorts suffering from this lethal infection. The exploration of the reasons why synergistic gangrene presents differently in different age groups unveils the etiological factors involved, where age might be the key factor in determining the severity of the disease.[7]

The harsh reality of synergistic gangrene is that it is an unconventional rapidly progressive microbial infection of elusive origins that silently engulfs the

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layers of skin and soft tissues with deadly consequences.[8] Despite the recent advances in medical knowledge, there remains a darth of understanding where this infection thrives demanding our attention towards the pathogenicity of the microbes and the faltering of the immune responses. The objective of this paper is to provide an in-depth exploration of the etiology of synergistic gangrene to understand the intricate interactions between the causative pathogens and the host factors including the immune responses that result in the onset and progression of this severe and rapidly progressive bacterial infection.

METHODOLOGY

This retrospective cross-sectional study design is conducted in two tertiary care hospitals. The duration of the study was four years (i.e. August 2019 to August 2023). The study participants were patients fulfilling the diagnostic criteria of synergistic gangrene who presented in the emergency departments of Sheikh Zayed Hospital. RYK & Combined military hospital, Bahawalpur. The study was conducted in accordance with ethical guidelines and approved by the ethical committee of Combined military hospital, Bahawalpur (ERC Ltr No.1516/EC/02/2023) and Institutional Review Board, Sheikh Zayed Medical College/hospital Rahim Yar Khan (Ref. No. 763/IRB/SZMC/SZH).

Patients of either gender with age ranging from 18 to 70 years, presenting in emergency departments fulfilling the diagnostic criteria of synergistic gangrene were included in the study. The criteria included soft tissue infections, presence of air at the subcutaneous wound margins, presence of necrotic/gangrenous tissue during wound debridement. Patients with localized abscess at site of injection or patients with incomplete follow-up or incomplete medical data were excluded from the study.

Raosoft sample size calculator was used to calculate the sample size of 169 with 95 % confidence interval and 5% margin of error. Sample size was adjusted to two hundred eighty-eight (288) for precision and accuracy.[9] The patients are divided into three age groups 18-30 years, 30-60 years, and >60 years. Data collection was done from medical records of the study period, patient histories, and clinical reports on various aspects like demography, clinical acumen, laboratory findings, and treatment modalities. Treatment modalities include surgical debridement, amputation, wound care (wound wash, dressing, and posture change), and combination therapy. All patients were given broad-spectrum intravenous antibiotics covering gram-negative, gram-positive, and anaerobic bacteria. It was recorded on self-constructed proforma.

Data analysis was performed by using a statistical package for the social sciences for Windows, version 20. Frequencies were calculated for quantitative variables. Chi-square test was used for the comparison of categorical variables. The $p<0.05$ was regarded as statistically significant.

RESULTS

Out of two hundred eighty-eight (n=288) patients male predominance was observed with one hundred eighty-nine (65.625%) males as compared to ninety-nine (34.375%) females. The majority belongs to the older age group above sixty years of age. Table-I.

Table-I: Gender Distribution Among Age Groups (n=288)

Age Group	Gender		Total (n=288)	*p*-value
	Male(n=189)	Female(n=99)		
18-30	30(16%)	19(19%)	47(16%)	0.325
31-60	76(40%)	31(31%)	109(38%)	
61+	83(44%)	49(49%)	132(46%)	

The risk factors of synergistic gangrene in different age groups include diabetes obesity, hypertension, STDs and addicts show significant values as shown in Table-II.

Table-II: Risk Factors for Synergistic Gangrene in Different Age Groups (n=288)

Risk Factor		18-30 Age (47)	31-60 Age (109)	61+ Age (132)	*p*-value
Diabetes	Yes	09(19.1%)	30(27.5%)	51(38.6%)	0.026
	No	38(80.9%)	79(72.5%)	81(61.4%)	
Peripheral Vascular Disease	Yes	05(10.6%)	17(15.5%)	22(16.7%)	0.610
	No	42(89.4%)	92(84.5%)	110(83.3%)	
Immunodeficiency (HIV, Steroid dependent, Malnutrition.)	Yes	05(10.6%)	10(9.1%)	12(9.1%)	0.948
	No	42(89.4%)	99(90.9%)	120(90.9%)	
Obesity	Yes	7(14.9)	13(11.9%)	05(3.7%)	0.021
	No	40(85.1%)	96(88.1%)	127(96.3%)	
Hypertension	Yes	03(6.4%)	22(20.2%)	27(20.5%)	0.075
	No	44(93.6%)	87(79.8%)	105(79.5%)	
Previous Skin Infections	Yes	2(4.3%)	4(3.6 %)	5(3.7%)	0.984
	No	45(95.7%)	105(96.4%)	127(96.3%)	
Sexually transmitted disease	Yes	5(10.6%)	9(8.3%)	2(1.5%)	0.018
	No	42(89.4%)	100(91.7%)	130(98.5%)	
Addicts	Yes	11(23.4%)	4(3.6%)	8(6.1%)	<0.001
	No	36(76.6%)	105(96.4%)	124(93.9%)	

"18-30," "31-60," and "61+" represent the age groups in years

Different bacterial isolates were predominant in different age groups as shown in Table-III. Also, the

synergistic gangrene affected body areas is different in different age groups as shown in the Table-IV.

Table-III: Distribution of Bacterial Isolates in Different Age Groups

Bacterial Isolate	18-30 (n=47)	31-60 (n=109)	61+ (n=132)
S. pyogenes	9(19%)	17(16%)	22(17%)
C. perfringens	6(13%)	29(27%)	20(15%)
E. coli	7(15%)	21(195)	18(14%)
MRSA	3(6%)	8(7%)	15(11%)
Bacteroides spp.	8(17%)	14(13%)	19(14%)
Streptococcus spp.	4(9%)	11(10%)	24(18%)
Polymicrobial	10(21%)	9(8%)	14(11%)

"18-30," "31-60," and "61+" represent the age groups in years

Table-IV: Clinical Presentation and Severity by Age Group

Age Group	Predominantly affected Body Area				Severity (Mild/Moderate/Severe)			
	Limbs n=86	Abdomen n=95	Perineum n=107	*p*-value	Mild n=57	Moderate n=117	Severe n=114	*p*-value
18-30 (n=47)	30(35%)	11(12%)	6(6%)	<0.001	13(23%)	21(18%)	13(11%)	<0.001
31-60 (n=109)	21(24%)	51(54%)	37(35%)		19(33%)	55(31%)	35(31%)	
61+ (n=132)	35(41%)	33(35%)	64(60%)		25(44%)	41(35%)	66(58%)	

"18-30," "31-60," and "61+" represent the age groups in years

In the majority of the cases, combination therapy was used as a treatment approach. A few of the patients were also underwent amputation as shown in Table-V.

Table-V: Immune Response, Treatment Options and Outcomes for Synergistic Gangrene

Treatment Approach	Age Group		
	18-30 (n=47)	31-60 (n=109)	61+ (n=132)
Surgical Debridement	14(30%)	37(34%)	41(31%)
Amputation	4(9%)	15(14%)	7(5%)
Wound Care	10(21%)	19(17%)	19(14%)
Combination Therapy	19(40%)	38(35%)	65(49%)
Immune Response	**Age Groups**		
Average WBC Count	14.4±2.51	10.8±2.03	16.2±3.03
C-Reactive Protein (mg/dl)	130±30	160±40	180±50

"18-30," "31-60," and "61+" represent the age groups in years

DISCUSSION

Synergistic gangrene is a polymicrobial fulminant infection with a predilection to perineal and abdominal regions. It leads to necrotizing fasciitis due to poor immunity with superadded infection and thrombosis of small subcutaneous blood vessels.[9]

The demographic distribution of patients in different age groups varies in terms of etiopathogenesis and disease patterns. The younger and middle age group had a higher proportion of males and the reason for the low prevalence of synergistic gangrene in females may be to better drainage of the genitourinary region by vaginal secretions. Our study showed the maximum number of patients in the older age group (p>0.3). Many studies have reflected age as an independent risk factor for prognosis.

On exploring literature Kappikeri *et al.,* shows that many predisposing factors like Diabetes mellitus, renal failure perianal disease, hemorrhoids, and urinary tract infections.[7] In our study, young Individuals with a strong history of Addiction and Diabetes mellitus are more prone to have this deadly infection. In the middle age groups, Diabetes and hypertension were the prevalent comorbidities. In the elderly group, diabetes Mellitus was the prominent underlying condition, followed by Hypertension and Peripheral vascular disease. This study affirmed the higher incidence in males and correlation with diabetes mellitus and Hypertension is the striking feature across all age groups. It endorsed the notion that males might be more prone to aggressive forms of the disease as found in a review study by Lewis *et al.*[10] This signifies the notion of considering age-related factors while diagnosing and treating synergistic gangrene, as it can have a significant impact on the management and outcome.[11]

The study delved into the impact of gender on the clinical pattern and morbidity of synergistic gangrene cases. Gender-specific patterns remains same across different age groups with male predominance. The maximum number of patients fell into the older age group. In the youngest age group, with a higher proportion of males, the disease was found to have a moderate course. Male patients within this group presented with predominant involvement of the limbs. This observation aligns with existing research by Abdullah Abbas *et al.,* that suggests a potential gender-related vulnerability to more aggressive forms of the disease.[12] In contrast, the middle age group exhibited moderate symptom severity, involving the abdomen and Perineum frequently. Among the elderly, the disease manifested

with severe symptoms affecting the perineal area with abdominal involvement subsequently. These patterns are suggestive of potential interplay between gender, age, and anatomical vulnerability, mandating further investigation.[13]

Popoff *et al.,* studied that Both Aerobic and anaerobic bacteriological organisms are isolated from the necrotic tissue due to poly microbial nature of this infection. The distribution of bacterial isolates showed a variable pattern among different age groups14. Mixed patterns were seen in younger age groups and more than one isolate was detected on culture including Bacteroides, streptococcus and MRSA etc. Clostridium perfringens (C. perfringens) and Escherichia coli (E. coli) were commonly detected in the middle age group a shown in a study by Rana *et al.*[15] Methicillin-resistant Staphylococcus aureus (MRSA) was detected across all age groups as shown by Rana *et al.,* with a slightly higher prevalence in the elderly. Streptococcus spp. and clostridial perfringens showed higher prevalence in the older age group of more than sixty years.[16] The study's identification of bacterial variations across age groups enlightened the medical landscape and its potential implications for disease management.

The clinical presentation and severity of synergistic gangrene showed variability among different age groups as studied by Joury *et al.*[17] Young adults often presented with moderate symptoms affecting the limbs. The associated comorbidity of addiction can be correlated to the limb involvement as the limbs are the preferred site for inadvertent pricks of narcotic/steroid injectables. The middle age group showed moderate severity with involvement of the abdomen. Elderly patients exhibited severe symptoms with involvement of the genital areas. The disease severity in older age groups may be correlated to poor immune response and diabetes. Tsuge *et al.,* proposed that these variation in symptom severity and affected body areas might reflect differences in immune response and overall health status among age groups.[18]

Laboratory investigations served as parameters of disease severity and immune response. The study gauged the white blood cell count and C-reactive protein levels in synergistic gangrene patients of different age groups. In the youngest age group, white blood cell counts were higher (14.4$\pm$2.51), indicating a prompt immune response to the infection. This heightened immune response reflects the onset of severe symptoms. Individuals in second group exhibited lower white blood cell counts, suggesting a comparatively less active immune reaction (10.8$\pm$2.03). In the elderly group, white blood cell counts were elevated (16.2$\pm$3.033), possibly the likely justification is an attempt to cope with the infection despite a potential decline in overall immunity. Correspondingly, C-reactive protein levels were recorded to objectively assess the severity, with the youngest age group (130$\pm$30) having the lowest levels and the oldest group (180$\pm$50) having the highest. All these findings resonate with established literature as seen by Broseghini *et al.,* emphasizing the importance of these lab biomarkers in assessing disease progression and making treatment decisions.[19]

The study explored the association between age and treatment outcomes. All the patients were receiving antibiotics as per standard protocol of infection. The young adults group demonstrated a higher antibiotic response rate but also a need for surgical intervention in most cases of synergistic gangrene. Majority of these patients warranted combination therapy including surgical debridement and wound care in addition to antibiotics. Middle-aged individuals needed surgical intervention in the form of combination therapy with surgical debridement to follow. Elderly patients had the highest white blood cell counts, indicating severe disease essentially needed a surgical debridement. This finding is in line with the published data by Elamragy *et al.*[20] Combination therapy along with antibiotics had relatively higher efficacy in the elderly group, possibly due to the complex and severe nature of cases in this age group.[21] The combination therapy included antibiotics, surgical debridement, and wound care remains the most effective treatment across all age groups. Limbs involvement paved the path for amputations in young age groups. The treatment approaches and outcomes and the varying utilization of surgical intervention with or without antibiotics reflects trends observed in clinical practice and aligns with notions of literature as by Beier *et al.,* endorsing for a multimodality approach to cope with deadly infection.[22] The variations in clinical presentation severity and immune response observed among different age groups and genders signify the tailored treatment strategy for individuals. The factors that can affect clinical decision-making are the anatomical areas affected but also the potential variations in immune response including white blood cell counts and C-reactive protein levels, in relation to

demography and Age. Personalized care strategies, while considering Age and disease severity can lead to improved recovery and better patient care in cases of synergistic gangrene as seen in a study by Joury *et al*.[23]

The mortality rate is variable range from 3-67% that reflects the multifactorial nature of this infection. Our study reports the mortality rate of 17% which coincides with literature by Shyam *et al*.[24] The high mortality may be denoted to large number of old age patients with less immunity and severe infections. Death resulted due to systemic illness, sepsis, acute renal failure and multiple organ failure.

Further research is warranted to delve deeper into the Predisposing factors driving these observed gender-specific and age-related differences in severity and immune response. Overall, this study's findings harmonize with existing research work and provide nuanced insights that contribute to a deeper understanding of synergistic gangrene's intricacies in relation to demographics, gender, severity, pathogen distribution, immune response, and treatment outcomes.

CONCLUSION

Synergistic gangrene is a fulminant necrotizing fasciitis that affects all age groups with male predominance with variable intensity. The younger and middle age males have predominant involvement of limbs and abdomen respectively with moderate intensity of symptoms contrarily older age group has severe disease with perineal involvement. Diabetes mellitus and Hypertension are the prevalent comorbidities among all age groups. The bacterial profiles vary by age from polymicrobial (young) to streptococcus and clostridia in old age patients. Combination therapy inclusive of debridement and wound care based on age and comorbidities remains the effective treatment. Further research is needed for exploration of age related disease patterns and treatment options and to refine the patient management protocols.

LIMITATIONS OF STUDY

While our study contributes insights into age-related risk factors for synergistic gangrene, it is important to acknowledge limitations such as the scope of the analyzed literature and potential bias in data reporting. Future research should aim for comprehensive cohort studies that directly investigate the role of age in synergistic gangrene etiology, enabling a more precise understanding of age-related risk factors.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KN & MSA: Data acquisition, data analysis, critical review, approval of the final version to be published.

DSM & MNA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FH & MAM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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