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Original Research Article

Efficacy of Adjunctive Low-Dose Ionizing Radiation Versus Standard Care in Reducing Mortality and Amputation Rates Among Patients with Gas Gangrene: A Systematic Review

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Abstract: ***Background:*** Clostridium-associated myonecrosis (gas gangrene) remains a rapidly fatal infection despite modern antibiotics, aggressive surgery, and hyperbaric oxygen therapy. ***Aim:*** This systematic review aims to critically evaluate historical and contemporary evidence regarding the therapeutic efficacy of low-dose ionizing radiation as an adjunctive treatment for Clostridium-associated myonecrosis (gas gangrene), specifically analyzing outcomes related to mortality reduction and limb preservation. ***Methods:*** A systematic search of PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and historical medical archives (1900–2025) was conducted following PRISMA guidelines. Eligible studies included human cases of clinically or bacteriologically confirmed gas gangrene treated with X-ray/roentgen therapy and reporting survival and/or amputation outcomes. Quality was appraised using Joanna Briggs Institute checklists for case series and case reports. ***Results:*** Six studies (predominantly pre-antibiotic era, all observational and uncontrolled) met inclusion criteria, encompassing up to 364 unique patients. Typical regimens delivered 75–150 R/day over several days using 90–100 kV for extremities and higher voltages for trunk lesions. Pooled mortality was approximately 11.5%, versus historical reference rates of 25–50% with surgery and serum therapy alone. Extremity cases treated early (within 24–48 hours) with multiple LDIR fractions showed the lowest mortality (as low as 4.3%) and reduced need for amputation, while concurrent antitoxin serum and delayed or limited irradiation were associated with poorer outcomes. ***Conclusion:*** Historical evidence suggests that adjunctive LDIR may substantially reduce mortality and amputation rates in gas gangrene, but the data are low quality and highly confounded. Rigorous modern preclinical and clinical studies are warranted to reassess LDIR as a potential adjunct in severe Clostridium myonecrosis.

Keywords: Amputation, Clostridium infections, Hyperbaric oxygenation, Mortality.

INTRODUCTION

Gas gangrene (GG), or clostridial myonecrosis, is a fulminant and lethal necrotizing soft tissue infection

(NSTI) caused predominantly by anaerobic, spore-forming bacteria such as Clostridium perfringens and Clostridium septicum (1). The condition is characterized by rapid microbial proliferation, extensive tissue necrosis, and the production of gas within tissue planes, driven by the release of potent exotoxins like alpha-toxin and perfringolysin O (1). These toxins disrupt cell membranes and trigger a cascade of systemic toxicity that can progress to septic shock within hours of onset. While traumatic injury remains the most common route of inoculation, spontaneous cases in immunocompromised individuals are increasingly recognized, posing significant diagnostic and therapeutic challenges (2).

Despite advancements in modern critical care, GG retains a catastrophic prognosis, with mortality rates ranging from 20% to nearly 100% in severe or untreated cases (3). The rapid progression of the infection often outpaces the efficacy of pharmacological interventions, leading to a "time-to-treatment" crisis where delays of even a few hours can be fatal. Furthermore, the profound systemic toxicity and massive tissue destruction frequently necessitate mutilating surgeries, including high-level amputations, to achieve source control. Survivors are often left with significant long-term disability, compounding the already substantial burden of the disease on healthcare systems and patient quality of life (2).

The current standard of care relies on a multimodal approach combining aggressive surgical debridement, broad-spectrum antibiotics, and, where available, hyperbaric oxygen therapy (HBOT) (1). Surgical intervention remains the cornerstone of management but is often radical, prioritizing life over limb preservation. Antibiotic therapy, while essential, faces growing concerns regarding efficacy against high bacterial loads in necrotic tissue where vascular delivery is compromised. Additionally, while HBOT can theoretically inhibit anaerobic bacterial growth and improve tissue oxygenation, its utility is limited by logistical constraints, lack of widespread availability, and the risks associated with transporting critically ill patients to specialized centers (2).

Given the persistently high morbidity and mortality associated with standard protocols, there is a compelling need to re-evaluate historical therapeutic adjuncts that may offer complementary benefits. Low-dose ionizing radiation (LDIR) was widely utilized in the pre-antibiotic era for its potential to arrest the spread of infection and reduce the need for amputation, yet it was largely abandoned following the advent of antimicrobial agents. This systematic review revisits the historical efficacy of LDIR to determine if this "forgotten" modality holds promise as a salvage therapy or adjunct in the modern era of antibiotic resistance. By synthesizing data from historical case series, this study aims to critically assess whether LDIR warrants renewed investigation as a strategy to improve survival and limb salvage rates in patients with GG.

MATERIALS AND METHODS

The literature was systematically searched up to 2025 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study process is illustrated in Figure 1.

2.1. Search strategies

To ensure a comprehensive aggregation of relevant literature, a systematic search was executed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Given the historical nature of the primary intervention, the search extended to digital archives such as the Historical Medical Library to access pre-antibiotic era literature (circa 1900–1950). Boolean operators were utilized to combine key terms relevant to the pathology and the intervention. Keywords included "Gas Gangrene," "Clostridium perfringens," "Clostridial Myonecrosis," "Low-Dose Radiation," "Roentgen Therapy," "X-ray Therapy," and "Radiotherapy." Reference lists of seminal reviews and identified articles were hand-searched to locate older, non-indexed case series. The search strategy was structured according to the PICOD framework (Population, Intervention, Comparison, Outcome, Design) to maximize relevance and specificity.

Table 1. Search strategies in the PICOD framework.

Element	Description
Population (P)	Patients diagnosed with gas gangrene (Clostridium myonecrosis) confirmed via clinical presentation or bacteriological culture.
Intervention (I)	Administration of low-dose ionizing radiation (X-ray/Roentgen therapy) applied directly to the affected site
Comparison (C)	Standard of care concurrent with the historical period (e.g., surgical debridement, amputation, serum therapy, or early antibiotics) without radiation.
Outcomes (O)	Primary outcomes: Mortality rate and incidence of amputation. Secondary outcomes: Symptom relief, speed of recovery, and cessation of gas production.

Design (D) Case series; Cohort study; Case report; Retrospective analysis; Clinical trial

2.2. Inclusion and exclusion criteria

Strict eligibility criteria were established to maintain the integrity of the review. Inclusion was limited to studies involving human subjects diagnosed with GG who underwent treatment with ionizing radiation, either as a monotherapy or in conjunction with surgery and serotherapy. Studies were required to report quantifiable clinical outcomes, specifically survival rates or limb salvage statistics. Both English-language publications and translated foreign literature (German, French) were considered, given the global prevalence of this therapy in the early 20th century.

Exclusion criteria encompassed studies focusing solely on dry or vascular gangrene (e.g., arteriosclerotic or diabetic gangrene without clostridial superinfection), as the pathophysiology differs significantly. Animal models were excluded from the primary efficacy analysis, though they were retained for discussions regarding biological mechanisms. Furthermore, articles lacking specific data points regarding dosage or clinical outcomes, as well as duplicate publications of the same patient cohorts (common in historical literature), were removed.

2.3. Quality assessment

For the quality assessment of included studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklists were employed, selecting the checklist for case series or case reports as appropriate to each study design. The JBI Checklist for Case Series evaluates key methodological domains, including the clarity of inclusion criteria, the reliability and standardization of condition measurement, the consecutive and complete inclusion of participants, the reporting of demographic and clinical information, the transparency of intervention details, the adequacy of outcome reporting, and the appropriateness of statistical analysis. For case reports, the JBI Checklist assesses the clarity of patient demographics, history, clinical presentation, diagnostic methods, intervention details, post-intervention outcomes, adverse events, and the overall completeness of the case description. These tools were chosen for their suitability in appraising non-comparative observational evidence and to ensure a systematic and transparent evaluation of study quality and risk of bias.

2.4. Data extraction

Data extraction was conducted to synthesize diverse clinical variables into a structured format. For each eligible study, the following data points were retrieved: first author and year of publication, study design, sample size, demographic characteristics of the population, and details of the radiation regimen (voltage, amperage, filtration, distance, total dose in Roentgens, and frequency of fractions). Critical clinical information extracted included the anatomical location of the infection (extremity vs. trunk), the type of concurrent surgical or medical therapy administered, and the timing of radiation relative to injury onset. Finally, quantitative outcome data were recorded, specifically the number of survivors, deaths, and amputations performed, to facilitate a comparative analysis of mortality rates against historical baselines.

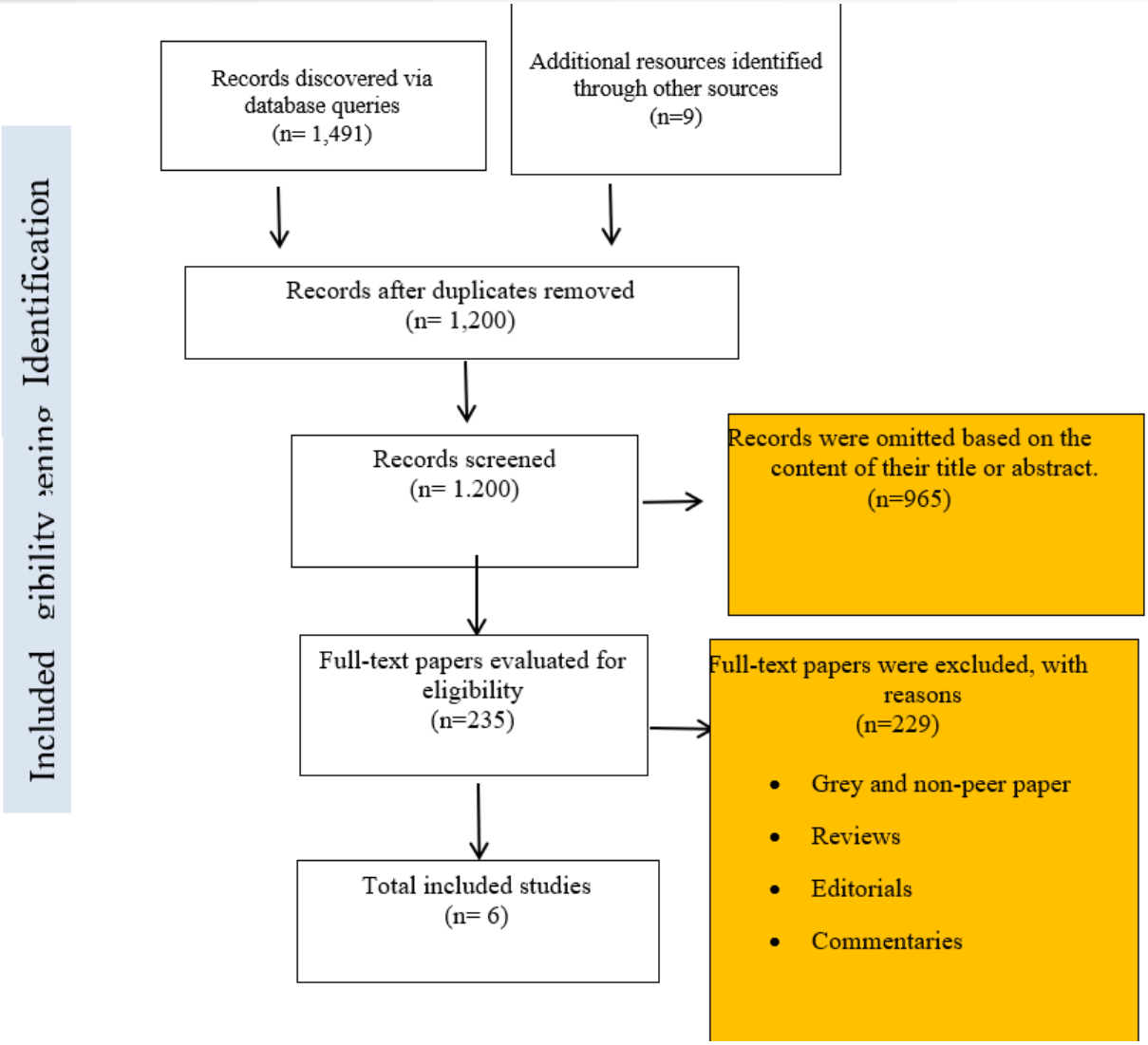
2.5. Ethics

As this research exclusively reviewed and synthesized data from previously published studies, it did not involve direct participation of human subjects or collection of primary data. Therefore, ethical approval and informed consent were not required.

RESULTS

1.1. Literature search

We retrieved 1,491 studies from different electronic databases, and an additional 9 records were found in an online search and via citation chaining. Consequently, 1,500 studies were retrieved in the initial search. All results were imported into Endnote X 9.2, and 1,200 studies remained after removing duplicates. After reviewing the title, abstract, and keywords, 965 articles were discarded without meeting the inclusion criteria, leaving 235 full-text articles for consideration. Out of 235 studies, 229 studies were excluded because they were reviews or editorials or gray and non-peer papers. Ultimately, six studies that met the inclusion and exclusion criteria were incorporated into this review. Figure 1 presents the assessment and selection processes for study selection according to PRISMA guidelines. Table 2 lists the characteristics of the six included studies.



The evidence base for adjunctive low-dose ionizing radiation in GG management comprises predominantly retrospective case series and descriptive reports from the pre-antibiotic and early sulfonamide eras. Six key publications met the inclusion criteria: four retrospective case series (Calabrese et al. 2012, summarizing historical data; Kelly et al. 1936; Faust et al. 1934; Godby 1940), one twelve-year retrospective review (Kelly & Dowell 1941), and one report containing two uncontrolled case descriptions (Caldwell & Cox 1941) (Table 2)

Table 2. Summary of the six selected articles.

Study Identification (Author/year)	Study design	Sample size	Anatomical Location	Radiation Regimen Details	Concurrent Therapy & Timing	Clinical Outcomes	Certainty assessment	Reference

Calabrese et al., 2012	Retrospective case series	N = 364, Age range: 8–82 years	Extremities: most common (leg, forearm). Trunk: less frequent (e.g., hernia-related). Some combined trunk/extremity cases	Voltage: 90–100 kV (extremities); 130–160 kV (trunk). Filtration: 0.5–1.0 mm aluminum (increased with voltage to prevent skin burns). Distance and mA not reported. Dose: Typically 150 R/day in: – 2 fractions of 75 R, or – 3 fractions of 50 R. Prophylactic dose: 75–150 R/day (single or repeated). Treatment duration: 3–13 days, adjusted by severity. Cumulative total dose: not standardized; ranged ~150–1950 R over course	Anti-toxin serum: used in 38/40 early cases; later, 18 cases received no serum. Surgery: debridement or amputation often delayed until after acute phase. Timing: X-rays initiated as soon as GG suspected, often within 24–48 hrs of injury. Concurrent use of surgery + serum + x-rays was typical in early reports	Overall mortality: 11.5% (42/364). With ≥3 x-ray treatments: mortality reportedly lower (exact % not given; only 42 patients in this subgroup). Amputations: 13/40 in early series (~32.5%); later reduced. Serum-free subgroup (n=18): 17 survived (5.5% mortality). All extremity cases in initial 6: 0% mortality, 0 amputations. Controls (historical): ~48–50% mortality pre-1930s; ~25% with improved surgical/serum care post-WWI	High	(4)
Caldwell & Cox, 1941	Two uncontrolled case reports (descriptive, critical of roentgen	n = 2; both male; ages 24 and 35 years	Right tibia (Case 1), Left tibia (Case 2) — both compound fractures	Case 1 only: 100 R per field, 2 fields, twice daily × 3 days (total 600 R delivered); technical parameters (kV, mA, filtration, distance) not reported	Case 1: Surgical incisions + sulfanilamide + serum initiated at 24h post-injury alongside radiation; amputation at 96h. Case 2: Wide debridement + H_2O_2 irrigation +	Mortality: 0/2 (0%); Amputation: 1/2 (50%); Infection controlled without amputation: 1/2 (50%). Radiation case failed to arrest infection despite multimodal therapy	Moderate	(5)

	ther apy)			for human use	sulfanilamide at ~36h post-injury; no radiation			
Kelly & Dowell, 1941	Retrospective twelve-year review and case series compilation of 364 post-traumatic GG cases.	N = 364	Of 364 cases: 303 (83.2 %) extremity involvement, 51 (14.0 %) trunk involvement, and 10 (2.7 %) undetermined location. Extremity cases had lower mortality (9.2 %) than trunk cases (27.5 %).	Technical factors: kV = 90–130 (higher for trunk); mA = ~5 mA (reported in Case 1); Filtration = "increased with kV", e.g., 0.5–1 mm Al or no filter; Distance = 40–50 cm. Dosimetry: Prophylactic = 75 R once daily × 3 days; Therapeutic = 150 R/day, typically as 2 × 75 R or 3 × 50 R fractions. Total therapeutic doses varied (e.g., Case 5: 525 R over 8 days).	Timing: X-ray started as soon as GG suspected, often within 24–96h post-injury; prophylaxis began within 48h of trauma. Adjunctive care: Surgery: Debridement rarely performed; 66/303 extremity cases (21.8%) had therapeutic amputation, discouraged during acute toxic phase. Serum: Antitoxins (e.g., Cl. welchii, tetanus) used in some cases but associated with higher mortality, especially in diabetics. Antibiotics: Sulfanilamide (oral/topical) used in some early cases (e.g., Cases 3–5),	Mortality: 42/364 deaths (11.5%) overall. Extremity: 28/303 (9.2%). Trunk: 14/51 (27.5%). Best subgroup: 2/46 (4.3%) with ≥3 x-ray treatments + no serum. Worst subgroup: 11/19 (57.9%) with 1 x-ray + serum. Limb Salvage: 66/303 extremity cases (21.8%) underwent amputation. Amputation mortality = 8/66 (12.1%). Non-amputation mortality = 15/176 (8.5%). Prophylaxis: 90 reported prophylactic cases.	High	(6)

					but explicitly discouraged due to antagonism with x-rays. X-ray withheld ≥12–24h after sulfonamide cessation.			
Godby, 1940	Retrospective case series	Total locally observed cases: 5	Case 1: Left femur/knee (extremity). Case 2: Right leg → thigh (extremity) Case 3: Left thigh → buttock/Poupart's ligament Case 4: Right shin (extremity) Case 5: Right leg (non-compound fracture with abrasions)	Voltage: 80 kV used locally by Godby (vs. Kelly's recommendation: 90–100 kV for extremities, 130–160 kV for trunk) Filtration: 1 mm Al for extremities Total Dose: ~100 R per field per dose Frequency: Twice daily for 3 days (6 total fractions); occasionally extended with 50 R/day Fields: Multiple fields to cover full infected area Note: In Case 1, popliteal space not irradiated due to splint	Antimicrobials: "Prontosil" (a sulfonamide) used in Cases 1, 3, and 5 Antitoxin/Serum: Anti-GG serum administered in Cases 1, 2, and 3 Surgical intervention: Case 1: Delayed surgical toilet (day 12), later amputation (day ~28). Case 2: Immediate extensive debridement, died within 48h. Case 3: Immediate surgical toilet, X-rays started on day 4. Case 4: No surgery reported, X-rays precautionary. Case 5: Below-knee amputation on contralateral side; infected leg	Local 5 cases: Survived (n=3): Cases 1 (limb lost but lived), 3, 4, 5 → 4 survivors. Died (n=1): Case 2. Amputated (n=2): Cases 1 & 5 (Case 5 amputated prior to infection). Kelly's series (Table I, Godby's summary): Extremity (n=105): 6 deaths → 5.7% mortality. Trunk (n=18): 4 deaths → 22.2% mortality. Diabetic/arteriosclerotic (n=9): 5 deaths → 55.6% mortality. Overall (n=132): 15 deaths → 11.3% mortality. Amputation comparison (Table II): Therapeutic amputation (for GG): 2/16 died →	Moderate	(7)

					managed non-operatively	12.5%. No amputation: 1/23 died → 4.3%. Suggests amputation for GG (vs. X-ray alone) associated with higher mortality		
Kelly et al., 1936	Retrospective case series	Total x-ray–treated cases: n = 40	Extremity: 28 cases (70%). Trunk: 8 cases (20%). Not specified/other: 4 cases (10%)	Original (1931) regimen: ~50–60 kV (5-inch spark gap), 5 mA, 0.5 mm Al filtration, 15-inch distance, 3 min BID × 3 days (dose not quantified). Recommended (1935) regimen: 90–100 kV (extremities), 130–160 kV (trunk), ~100 R per fraction, BID for ≥3 days. Some fatal cases received only 100 R (Day 1) + 90 R (Day 2)	Adjunctive care: GG antiserum (38/40, 2 without serum survived), local antiseptics. Surgery: Amputation in 13/40 (32.5%), minor surgery/debridement implied otherwise. Timing: Radiation started "as soon as disease suspected"; no precise time from injury/onset reported	Mortality: 7/40 deaths (17.5%); 4/40 (10%) directly due to GG. Extremity subgroup (n = 28): 5 deaths (17.9%), all in amputated patients (5/11 = 45.5%); 0/17 deaths in non-amputated Trunk subgroup (n = 8): 0 deaths. Limb salvage: 17/28 (60.7%) extremity cases avoided amputation and all survived	Moderate	(8)

Faust et al., 1934	Case series	N = 5 Case 1: 15-year-old male Case 2: 66-year-old female Case 3: 72-year-old male Case 4: 20-year-old male Case 5: 21-year-old female	Case 1: Right leg Case 2: Left forearm → amputation at upper arm; also pectoral muscles Case 3: Forearm (triceps, ulnar/radial nerves) Case 4: Abdomen (right rectus) and left axilla Case 5: Abdominal incision (post-appendectomy/salpingectomy)	Spark gap: 5-inch. Amperage: 5 mA. Distance: 40 cm (target to skin). Filtration: 0.5 mm aluminum. Exposure time: 3 minutes per field. Fractionation: Variable, Case 1: 8 treatments, Case 2: 10 treatments over 6 days, Case 3: 6 treatments, Case 4: 8 + 3 treatments (right then left), Case 5: 8 treatments over 4 days	Antitoxin (GG serum): Case 1: Administered, Case 2: Administered, Case 3: Administered twice, Case 4: Administered twice initially; none for left axilla recurrence, Case 5: One dose, Surgical interventions: Debridement, suturing, drainage, or amputation as clinically indicated (e.g., Case 2: amputation; Case 4: primary closure with drain), Timing: Radiation initiated upon confirmation of GG (within 24–72 hours of symptom onset)	All 5 patients survived (0% mortality). Amputation occurred only in Case 2 (1/5 = 20%), performed before radiation due to extensive necrosis. Limb salvage in extremity cases: 3/4 (Cases 1, 3, 4 [right side]); Case 2 already amputated. Resolution of gas/crepitus confirmed radiographically or clinically in all cases. Temperature normalized (<100°F) in all within days of starting therapy. Wound healing achieved in all. Hospital stay: 2–8 weeks (exact duration for all not uniformly reported)	Moderate	(9)

Across these reports, a total of 364 patients are described in the large Kelly & Dowell series and its historical reconstructions (overlapping with Calabrese et al.), with smaller local cohorts (n = 5–40) in the remaining studies. All studies are uncontrolled, non-randomized, and observational, with substantial heterogeneity in radiotherapy

parameters, timing, and concurrent therapies. Nonetheless, they consistently report on key outcomes relevant to this review: mortality, need for amputation, and qualitative resolution of infection.

1.2. Low-Dose Ionizing Radiation

1.2.1. Radiation Regimens and Adjunctive Therapies

Radiation regimens across studies were generally consistent in employing low-dose x-rays, typically in the range of 75–150 R per day, fractionated over several days. Calabrese et al. (2012) (4), and Kelly & Dowell (1941) (6), both described regimens of 90–100 kV for extremities and higher voltages for trunk involvement, with filtration adjusted to minimize skin toxicity. The cumulative doses varied widely, from approximately 150 R to nearly 2000 R, depending on disease severity and response. Adjunctive therapies included anti-toxin serum, surgical debridement or amputation, and, in some cases, early antibiotics such as sulfonamides. Notably, the timing of radiation was emphasized as critical, with most studies initiating therapy within 24–48 hours of clinical suspicion or confirmation of GG (4, 6, 8).

1.2.2. Mortality Outcomes

Across the included studies, adjunctive low-dose ionizing radiation was associated with a marked reduction in mortality compared to historical controls. Calabrese et al. (2012) reported an overall mortality of 11.5% (42/364), a substantial improvement over pre-1930s rates of 48–50% and even over the 25% mortality observed with improved surgical and serum care post-World War I (4). Similarly, Kelly & Dowell (1941) documented an overall mortality of 11.5% in their 364-case series, with extremity cases faring better (9.2%) than trunk cases (27.5%). Subgroup analysis revealed that patients receiving three or more x-ray treatments without serum had the lowest mortality (4.3%), while those receiving only one x-ray and serum had the highest (57.9%) (6).

Godby (1940) observed a comparable overall mortality of 11.3% in a combined analysis of local and referenced cases, with extremity involvement associated with lower mortality (5.7%) than trunk involvement (22.2%) (7). In the smaller series by Kelly et al. (1936), the mortality rate was 17.5% (7/40), with all deaths occurring in amputated patients (8). Faust et al. (1934) reported no deaths among five treated patients (9), while Caldwell & Cox (1941) described two cases, both surviving, though one required amputation despite radiation (5).

1.2.3. Limb Salvage and Amputation Rates

Limb preservation was a key outcome in these studies. Calabrese et al. (2012) noted a reduction in amputation rates over time, with 13 of 40 early cases (32.5%) requiring amputation, a figure that decreased as experience with radiation therapy increased (4). In the Kelly & Dowell (1941) series, 21.8% (66/303) of extremity cases underwent amputation, with a lower mortality among non-amputated patients (8.5%) compared to those who underwent amputation (12.1%) (6). Godby (1940) found that amputation for GG was associated with higher mortality (12.5%) compared to cases managed without amputation (4.3%), suggesting a potential limb-sparing benefit of adjunctive radiation (7).

In the Kelly et al. (1936) cohort, 60.7% of extremity cases avoided amputation and all survived, while all deaths occurred in the amputated subgroup (8). Faust et al. (1934) reported limb salvage in three of four extremity cases, with the only amputation performed prior to radiation due to extensive necrosis (9). Caldwell & Cox (1941) described one case where infection was controlled without amputation and another where amputation was required despite multimodal therapy, including radiation (5).

1.2.4. Timing and Integration of Therapies

The timing of radiation initiation emerged as a critical factor. Most studies emphasized the importance of starting x-ray therapy as soon as GG was suspected, often within the first 24–48 hours post-injury. Adjunctive use of anti-toxin serum and surgery was common, though some evidence suggested that serum use, particularly in diabetic patients, was associated with higher mortality (6). The use of sulfonamides was discouraged in combination with radiation due to potential antagonism.

1.3. Clostridium perfringens (CP)

Clostridium perfringens (CP), a bacterium identified by William Welch in 1891, is a significant pathogen associated with a range of illnesses, from mild food poisoning to severe situations like GG (10). This organism was originally designated as Bacillus aerogenes capsulatus (11). It was then called Bacillus perfringens and subsequently Clostridium welchii (10-12). It is presently designated as Clostridium perfringens, a spore-forming Gram-positive anaerobic bacillus (12). The prevalence of CP in the United States is around 1000–3000 cases annually, with a death rate varying from 30% in non-immunocompromised individuals to 67% in immunocompromised people (2, 11, 13). Consequently, comprehending the many forms of GG and its fundamental genesis is essential for precise diagnosis

and effective care. Cerebral palsy manifests in two primary forms: traumatic and spontaneous (2). Traumatic GG is the predominant variant and generally occurs after to traumatic traumas that introduce CP spores into deep tissue (11, 14). These injuries may arise from trauma, including crush injuries, compound fractures, or piercing wounds, particularly those incurred during severe incidents such as motor vehicle crashes or industrial accidents (15). Spontaneous or hematogenous GG, induced by Clostridium septicum or Clostridium novyi, arises in the absence of apparent external injury and is frequently linked to underlying medical conditions or predisposing factors that promote bacterial spread, including immunocompromised states, malignancy, and vascular insufficiency (2).

1.3.1.Pathogenicity

The 632 strains of C. perfringens were categorized into seven kinds (A–G) according to the most recent classification update. C. perfringens contains a singular circular chromosome with a size ranging from 2.9 to 4.1 Mb (16). It encodes an estimated 2600 to 3800 putative genes (17). CP necessitates numerous vital nutrients and amino acids for growth, as demonstrated by genome sequencing, which shows an absence of genes for the production of certain amino acids and the tricarboxylic acid cycle (17, 18). The genome encodes degradative enzymes, including sialidases, as well as a comprehensive array of enzymes for fermentation and glycolytic pathways, allowing the bacteria to metabolize complex host polysaccharides by hydrolyzing them into simple sugars (17, 18).

The CP genome comprises around 200 transport-related genes, including ABC transporters, which enable the absorption of carbohydrates, amino acids, nucleotides, and ions from the host environment (17). These transporters assist the bacterium in compensating for its inability to generate vital nutrients by obtaining them from host tissue. Moreover, the genome contains several rRNA operons and tRNAs, facilitating the fast synthesis of released enzymes and poisons (18). The organism's rapid growth capability is a crucial element of its pathogenicity and its competitive advantage over other bacteria in decomposing dead tissue.

Plasmids are crucial in the pathogenicity of CP, especially in intestinal disorders (17, 18). These extrachromosomal DNA fragments possess genes that augment the bacterium's virulence and adaptability. CP plasmids are classified into three principal families according to the genes that initiate plasmid DNA replication: pCW3-like, pCP13-like, and pIP404-like plasmids (13, 17, 18).

The plasmids belonging to the pCW3-like family are conjugative, indicating their ability to transfer across bacterial cells via direct contact. This capability promotes the dissemination of virulence factors within CP populations }(18). pCW3-like plasmids frequently harbor genes that encode toxins, provide antibiotic resistance, and possess additional elements that augment bacterial survival and virulence within the host environment (17, 18). Like the pCW3-like family, pCP13-like plasmids are likewise conjugative. They are crucial to horizontal gene transfer, enhancing the genetic diversity and adaptability of CP (19). These plasmids may contain genes for enterotoxins, which are essential in food poisoning and other gastrointestinal illnesses induced by CP (20). The conjugative properties of these plasmids facilitate the fast spread of virulence genes throughout bacterial populations (19).

Conversely, pIP404-like plasmids are non-conjugative, indicating that they cannot be transferred between bacterial cells by conjugation (19). Notwithstanding this limitation, they continue to exert a considerable influence on the pathogenicity of CP. These plasmids can harbor genes that enhance the bacterium's pathogenicity, including those encoding toxins and other virulence determinants. Their multiplication within a bacterial cell can augment the overall virulence and survival abilities of CP (13). The existence of these plasmids in CP markedly amplifies its pathogenicity. They encode several virulence factors, encompassing poisons, antibiotic resistance, and mechanisms for adaptation and survival. Numerous plasmids have genes for powerful toxins, including enterotoxins and beta toxins, which are accountable for the severe manifestations of food poisoning and GG (17, 19). Certain plasmids contain genes that bestow antibiotic resistance, complicating treatment alternatives and facilitating the persistence of infections. Moreover, plasmids augment the bacterium's capacity to acclimatize to various environmental conditions, including those present within the host, thereby improving its survival and proliferation (19).

The cpe gene, which encodes CP enterotoxin (CPE), is distinctive as it can reside on either the chromosome or plasmids (2). Approximately 70% of type F human food poisoning isolates possess their cpe genes on the chromosome (21). In these instances, the gene is frequently bordered by IS1470 sequences, indicating that the chromosomal existence of the cpe gene may stem from the incorporation of a cpe-bearing transposon (17, 22). Thirty percent of type F food poisoning strains, predominantly type F non-food-borne human gastrointestinal disease strains, together with cpe-positive type C, D, and E strains, possess their cpe genes on large pCW3-like conjugative plasmids (17, 21). In type F strains, the cpe plasmids mostly group into two subfamilies: pCPF4969-like plasmids and pCPF5603-like plasmids (17). The pCPF4969-like plasmids lack the cpb2 gene, whereas the

pCPF5603-like plasmids have the cpb2 gene (17, 21).

Initially, CP spores are crucial to its pathogenesis (20). These spores demonstrate resilience to heat, cold, osmotic pressure, chemicals, and severe pH levels, hence enhancing CP's survival across diverse environments, especially in type C and F strains (17). A crucial element in the spores' resilience is the existence of α/β-type small acid-soluble proteins (SASPs), which attach to the spore's DNA, protecting it from environmental stressors (20, 23). CP generates four principal SASPs, each enhancing spore robustness to heat, chemicals, and UV radiation (23).

CP infiltrates tissue by several routes, including inadvertent traumatic injuries (e.g., complex fractures, penetrating combat injuries, surgical incisions from operations such as bowel or biliary system surgery, or septic abortions) (17, 23). CP infection infrequently arises in conjunction with arterial insufficiency or subsequent to the parenteral administration of substances such as aqueous epinephrine, subcutaneous insulin, or narcotics like methamphetamine and heroin. CP has further complicated standard medical procedures such as venipuncture or platelet infusions in patients with granulocytopenia (2).

In many instances, CP disseminates in the circulation, causing an infection without considerable tissue damage, frequently linked to intestinal tract anomalies such as colon cancer, diverticulitis, or bowel infarction. Predisposing factors encompass leukemia, neutropenia, and diabetes mellitus. The bacterium likely infiltrates by mucosal ulceration or perforation in the digestive system, occasionally resulting in swift multifocal muscle involvement or profound tissue damage. The local tissue dispersion of CP amplifies the synthesis of virulence components (24).

The interplay between toxin synthesis (with a minimal lethal dose in animals of 10^{10}), enzymatic functions (such as proteases, hyaluronidase, collagenase, sialidases, and endoglycosidases), and additional virulence determinants results in significant tissue necrosis. Certain poisons produce localized tissue effects, whilst others induce systemic effects including hemolysis, intravascular thrombosis, and cytokine release. This cascade may result in shock, multi-organ failure, and eventually mortality. The following section discusses various CP toxins and their methods of action (Figure 2) (2).

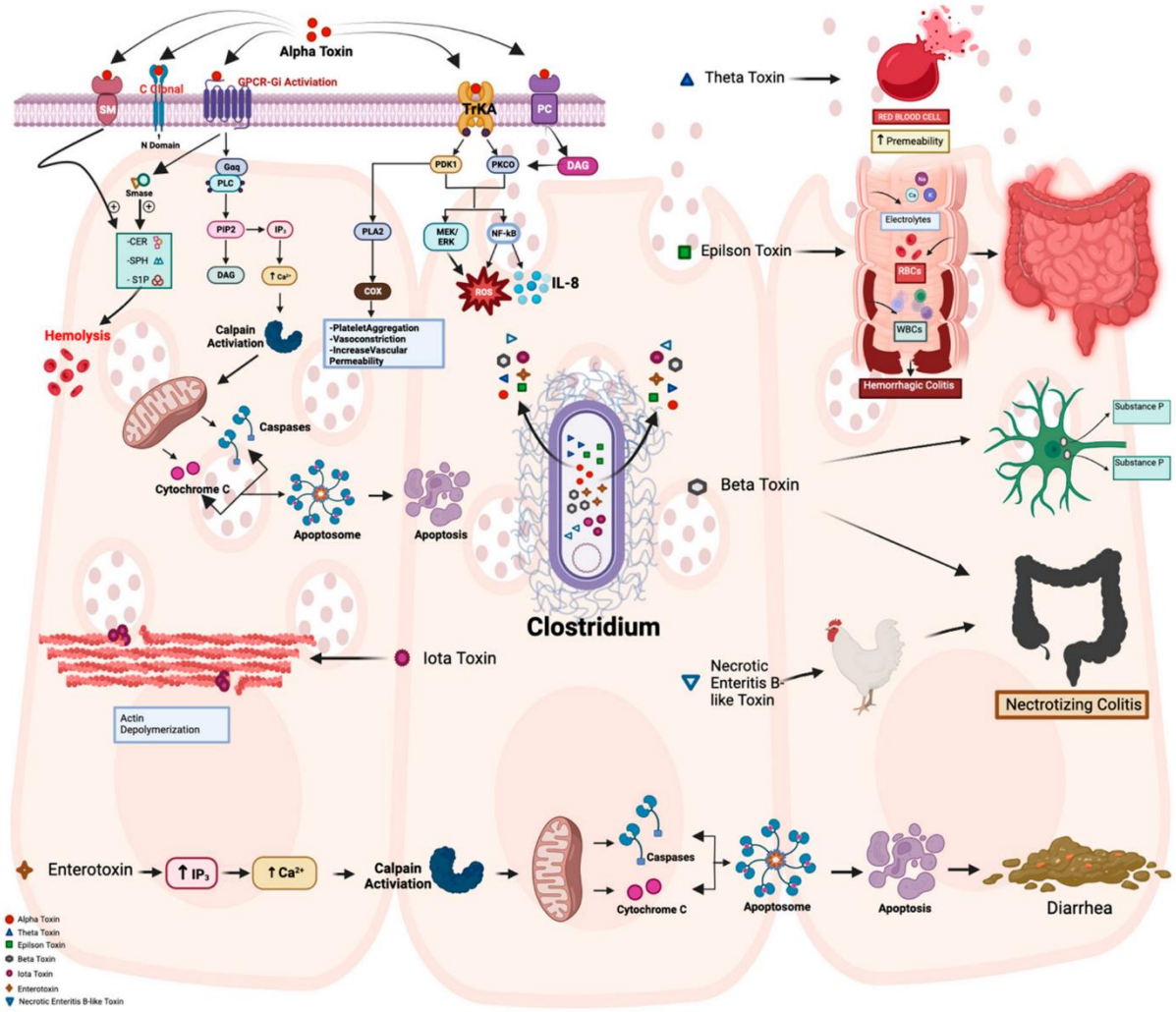


Figure 2. Virulence factors of Clostridium and their modes of action.

Alpha toxin specifically targets the plasma membranes of host cells, hydrolyzing sphingomyelin and phosphatidylcholine, which then activates phospholipases and sphingomyelinases, resulting in calcium influx, calpain activation, and cellular necrosis. Alpha toxin interacts with Gi-GTP-BP and TrkA receptors, triggering signaling cascades that involve MAPK/ERK and NF-κB, leading to the creation of ROS and IL-8, as well as vascular consequences. Theta toxin interacts with cholesterol to create β-barrel pores, resulting in the lysis of red blood cells. Epsilon toxin forms heptameric holes, disrupting ion equilibrium and inducing caspase-independent cell death, resulting in enterocolitis. Beta toxin impacts neurons and colonic mucosa, prompting catecholamine release, artery constriction, and TNF-α-mediated plasma extravasation, which leads to necrotic cell death and necrotizing enterocolitis. Iota toxin ADP-ribosylates actin, resulting in cellular apoptosis. Enterotoxins compromise intestinal mucosal tight junctions, create β-barrel holes, and induce calcium influx, resulting in calpain activation, necrosis, apoptosis, and diarrhea. In hens, necrotic enteritis beta-like toxin creates heptameric holes, resulting in osmotic cell lysis. Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK); nuclear factor kappa B (NF-kB); Gi-type GTP-binding protein (Gi-GTP-BP); reactive oxygen species (ROS); interleukin (IL); tumor necrosis factor (TNF); adenosine diphosphate (ADP) (2).

1.3.2. Types of CG

Comprehending the many forms of GG and their underlying etiology is essential for precise diagnosis and effective management.

1.3.2.1. Traumatic Gas Gangrene

Traumatic GG is a serious and swiftly advancing infection predominantly attributed to CP, representing more than 80% of instances (25, 26). Other *Clostridium* species, such as *Clostridium septicum*, *Clostridium novyi type A*, and *Clostridium histolyticum*, can also induce similar infections, though less frequently (27). Infections generally arise

after traumatic injuries, including crush injuries, compound fractures, or piercing wounds, wherein CP spores infiltrate devitalized tissue, establishing an anaerobic milieu conducive to bacterial proliferation and toxin synthesis (2).

The etiology of traumatic GG encompasses multiple pathways, including toxin-induced microvascular thrombosis. This process diminishes tissue perfusion, resulting in hypoxia and the ensuing necrosis of the afflicted tissue (2). The clinical manifestations encompass intense pain that is incongruent with physical findings, swift tissue necrosis, gas accumulation within tissue (comprising 5.9% hydrogen, 3.4% carbon dioxide, 74.5% nitrogen, and 16.1% oxygen), and systemic toxicity characterized by fever, tachycardia, hypotension, and shock (26, 27). Treatment necessitates urgent surgical intervention to excise necrotic tissue and diminish the bacterial burden, alongside high-dose antibiotics aimed at anaerobic bacteria such as CP (25). Hyperbaric oxygen therapy may serve to augment tissue oxygenation and suppress bacterial proliferation. Timely diagnosis and intervention are essential to avert systemic consequences including sepsis, multi-organ failure, and mortality. A comparison to acute arterial thrombosis, characterized by severe pain and tissue necrosis resulting from blood supply obstruction, highlights the urgency of GG and the necessity for prompt medical intervention to maintain tissue viability and ensure patient survival (2).

The clinical manifestation of traumatic GG is characterized by intense pain that is disproportionate to physical examination results, swiftly advancing tissue necrosis, and the detection of crepitus (gas bubbles) beneath the skin (25, 26). Systemic consequences may encompass fever, tachycardia, hypotension, and shock resulting from toxins generated by the bacteria. Diagnosis is predominantly clinical, corroborated by imaging techniques including X-rays or CT scans revealing gas in the afflicted tissue, alongside test results indicating leukocytosis and metabolic acidosis (2).

The management of traumatic GG is urgent and entails surgical investigation and debridement to excise necrotic tissue and diminish the bacterial burden (25). Antibiotic treatment aimed at anaerobic bacteria, including high-dose penicillin or broad-spectrum agents such as carbapenems or clindamycin, is crucial. Hyperbaric oxygen therapy may be utilized as an adjuvant to improve tissue oxygenation, suppress anaerobic bacterial proliferation, and facilitate wound healing (28).

The ramifications of untreated or insufficiently managed GG can be grave, encompassing limb amputation, septic shock, multi-organ failure, and mortality (29). The prognosis significantly depends on early diagnosis and the swift commencement of treatment. Prevention measures underscore rigorous wound management, encompassing comprehensive cleansing and debridement of traumatic or surgical wounds to reduce bacterial infection (25). In high-risk scenarios, such as infected wounds or immunocompromised individuals, prophylactic antibiotics may be deemed appropriate. Current investigations with vaccinations aimed at Clostridium species show potential for future preventive strategies against traumatic GG (30, 31).

1.3.2.2. Spontaneous or Hematogenous Gas Gangrene

Spontaneous or hematogenous GG contrasts with traumatic GG in its etiological factors and clinical manifestations (17, 25). It generally originates from the hematogenous dissemination of bacteria, particularly Clostridium species such as CS, from a main site of infection or colonization. Other Clostridium species, such as CP, CN type A, and Clostridium histolyticum, may also be implicated, though less commonly (25).

Prevalent origins encompass gastrointestinal cancers, colonic diverticulitis, or other gastrointestinal disorders (25). Individuals with weakened immune systems, such as those receiving chemotherapy or exhibiting poorly managed diabetic mellitus, are especially prone to the onset of spontaneous GG due to their heightened susceptibility to bacterial spread (25, 32). Clinically, spontaneous GG may manifest with a more gradual onset in contrast to traumatic GG (33). Patients frequently have systemic manifestations including fever, chills, and malaise, indicative of hematogenous bacterial spread and systemic toxin effects (33). Localized symptoms encompass discomfort, swelling, and indications of tissue necrosis at the infection site, which worsen progressively as the infection advances. The diagnosis of spontaneous GG is contingent upon clinical suspicion, particularly in patients with preexisting malignancies or immunosuppressive diseases who exhibit indications of tissue necrosis and gas formation (25). Imaging investigations, including CT scans, can detect gas within tissue, facilitating diagnosis and evaluating the level of tissue involvement. Microbiological cultures of blood and damaged tissue verify the presence of Clostridium species and inform antibiotic treatment (2).

Treatment necessitates immediate surgical intervention to excise necrotic tissue and eliminate the infection source (14). Empirical antibiotic therapy aimed at anaerobic bacteria, commenced with high-dose penicillin,

cephalosporins, or carbapenems, is crucial and modified according to culture results (25, 33). Moreover, clindamycin or linezolid assists in inhibiting toxin generation or its impact on the tissue. Supportive therapy encompasses vigorous fluid resuscitation and the management of systemic symptoms (2).

The prognosis is contingent upon early diagnosis and the swift commencement of treatment. Mortality rates may be elevated, especially in immunocompromised individuals or those with advanced malignancies. Complications including sepsis, multi-organ failure, and mortality underscore the necessity for prompt and thorough care (2).

1.3.3.Epidemiology

In the United States, myonecrosis occurs in approximately 1000–3000 instances annually, although the global incidence is about 0.4 per 100,000 per year (13). GG has always been acknowledged for its substantial prevalence during conflict, with comparatively few civilian instances documented. In World War I, GG complicated about 6% of open fractures and 1% of all open wounds, indicating its frequency in wartime settings. In succeeding conflicts, such as World War II, the Korean War, and the Vietnam War, the incidence progressively diminished to 0.7% and 0.2%, ultimately down to 0.002%, respectively (34). By the Falklands War in 1982, no instances of GG were documented, underscoring improvements in trauma treatment, antibiotics, and wound management that led to diminished infection rates in contemporary military environments (34).

A study comparing survival periods following the beginning of traumatic and non-traumatic GG revealed that patients with traumatic GG had an average survival time of 15 hours, whereas those with non-traumatic GG had a markedly reduced average survival time of 8 hours (13, 25). This underscores the essential significance of GG, especially in non-traumatic instances, which may advance more swiftly, potentially because to the earlier systemic spread of germs or pre-existing disorders that predispose individuals to infection. In a survey of 1,970 earthquake survivors, GG was noted in 0.96% of individuals (13). A separate study with 226 patients from the same earthquake emphasized the significance of prompt screening, isolation, surgical debridement, amputation when required, and intensive supportive care for effective disease management and containment (35).

A research on GG patients revealed an 80% mortality rate, in stark contrast to the 0% mortality rate observed in necrotizing fasciitis patients, where limb salvage was achieved in eight instances, resulting in one amputation. With optimal care, encompassing early discovery, surgical intervention, antibiotic medication, and hyperbaric oxygen treatment, the death rate varies from 20% to 30%, with some studies reporting figures as low as 5% to 10% (13). If not addressed, the disease is invariably lethal. Specific host variables, including immunocompromised conditions, diabetes mellitus, and spontaneous infections, can increase mortality rates to 67% or more. Infections of the abdomen soft tissue or chest wall can yield fatality rates reaching 60%, in stark contrast to extremities infections, which exhibit more favorable mortality rates of 5% to 30% (13).

1.3.4.Treatment

Management of GG involves aggressive surgical and medical interventions to swiftly control infection, mitigate toxin production, and avert systemic complications (2). Empirical antibiotic protocols typically incorporate broad-spectrum agents such as piperacillin-tazobactam, ceftriaxone, or penicillin G, often in conjunction with clindamycin or linezolid to suppress toxin production, and metronidazole for anaerobic coverage; vancomycin or carbapenems like meropenem are utilized in severe or immunocompromised scenarios to guarantee coverage against resistant pathogens and polymicrobial infections (36, 37). Antitoxin therapy, such as alpha antitoxin and antitoxin IgY targeting specific clostridial toxins, may be employed in particular severe or refractory cases, however their availability and indications are restricted. The rise of antibiotic resistance in Clostridium species, particularly involving resistance genes like erm(T) and ant(6)-Ib, highlights the necessity for monitoring and the creation of alternative or supplementary treatments (38, 39).

The surgical approach focuses on the immediate and comprehensive debridement of all necrotic and devitalized tissue to eliminate the anaerobic conditions that facilitate clostridial growth and toxin synthesis (13, 40). This is succeeded by extensive irrigation, meticulous hemostasis, and, where warranted, fasciotomy to alleviate compartment pressure and maintain limb viability (40). Negative pressure wound care facilitates wound healing and diminishes the risk of secondary infection, with subsequent reconstructive surgeries or skin grafting contemplated once infection is managed and viable tissue margins are evident (40). Successful outcomes typically necessitate collaborative care among surgeons, infectious disease specialists, anesthesiologists, and critical care clinicians in an intensive care environment for meticulous hemodynamic and organ function monitoring (40).

Hyperbaric oxygen therapy (HBOT) functions as an adjuvant treatment that elevates tissue oxygen levels, consequently suppressing anaerobic clostridial proliferation and augmenting the bactericidal efficacy of reactive

oxygen species (28, 41). HBOT enhances tissue perfusion, stimulates angiogenesis, and supports fibroblast function, hence facilitating wound healing, minimizing further tissue necrosis, and decreasing the risk of amputation when administered with timely debridement and suitable antibiotics (28, 41). Rehabilitation following GG entails organized physical therapy, careful wound management, psychological assistance, and functional training with assistive devices to regain mobility and autonomy, while nutritional support and consistent outpatient follow-up enhance long-term recovery and quality of life (42, 43).

Future strategies in GG management emphasize enhanced toxin neutralization and host support. Research efforts encompass monoclonal antibodies, small-molecule inhibitors, and peptide decoys aimed at clostridial toxins, in addition to bacteriophage therapy to specifically diminish clostridial load without exclusively depending on traditional antibiotics (44, 45). Current research includes immunomodulators that adjust the inflammatory response, vaccines targeting clostridial toxins, regenerative methods like post-debridement stem cell transplantation for tissue repair, and targeted therapies such as proton radiation to manage localized infections while preserving healthy tissue. Clinical case studies generally indicate that early diagnosis, prompt broad-spectrum antibiotic treatment, timely surgical intervention, and, when applicable, hyperbaric oxygen therapy (HBOT) are crucial for enhancing survival and functional outcomes in Clostridium myonecrosis (46, 47).

Table S1. Search strategies in databases.

	Search ID#	**Search terms**	**Results**
PubMed	#1	(((((Gas Gangrene[Title/Abstract]) OR (Gangrene, Gas[Title/Abstract])) OR (Gangrenes, Gas[Title/Abstract])) OR (Gas Gangrenes[Title/Abstract])) OR (Clostridium perfringens[Title/Abstract])) OR (Clostridium welchii[Title/Abstract])	11,353
	#2	((((((((((((((Radiotherapy[Title/Abstract]) OR (Radiation Therapy[Title/Abstract])) OR (Radiation Therapy, Targeted[Title/Abstract])) OR (Radiation Treatment[Title/Abstract])) OR (Radiotherapy, Targeted[Title/Abstract])) OR (Targeted Radiation Therapy[Title/Abstract])) OR (Targeted Radiotherapy[Title/Abstract])) OR (X-Ray Therapy[Title/Abstract])) OR (X-Rays[Title/Abstract])) OR (Roentgenotherapy[Title/Abstract])) OR (Therapy, X Ray[Title/Abstract])) OR (Therapy, Xray[Title/Abstract])) OR (Xray Therapy[Title/Abstract])) OR (low dose[Title/Abstract])) OR (low dose radiation[Title/Abstract])) OR (low dose computed tomography[Title/Abstract])) OR (low dose ct[Title/Abstract])	560,588
	#3	#1 AND #2	73
Scopus	#1	(TITLE-ABS-KEY (Gas Gangrene) OR TITLE-ABS-KEY (Gangrene , Gas) OR TITLE-ABS-KEY (Gangrenes , Gas) OR TITLE-ABS-KEY (Gas Gangrenes) OR TITLE-ABS-KEY (Clostridium perfringens) OR TITLE-ABS-KEY (Clostridium welchii))	20,722
	#2	(TITLE-ABS-KEY (Radiotherapy) OR TITLE-ABS-KEY (Radiation Therapy) OR TITLE-ABS-KEY (Radiation Therapy Targeted) OR TITLE-ABS-KEY (Radiation Treatment) OR TITLE-ABS-KEY (Radiotherapy Targeted) OR TITLE-ABS-KEY (Targeted Radiation Therapy) OR TITLE-ABS-KEY (Targeted Radiotherapy) OR TITLE-ABS-KEY (X-Ray Therapy) OR TITLE-ABS-KEY (X-Rays) OR TITLE-ABS-KEY (Roentgenotherapy) OR TITLE-ABS-KEY (Therapy X Ray) OR TITLE-ABS-KEY (Therapy Xray) OR TITLE-ABS-KEY (Xray Therapy) OR TITLE-ABS-KEY (low dose) OR TITLE-ABS-KEY (low dose radiation) OR TITLE-ABS-KEY (low dose computed tomography) OR TITLE-ABS-KEY (low dose ct))	4,130,863
	#3	#1 AND #2	955
EMBASE	#1	('gas gangrene'/exp OR 'clostridium perfringens infection'/exp OR 'clostridium welchii infection'/exp OR 'gas gangrene':ab,ti OR	3,112

		'gangrene, gas':ab,ti OR 'gangrenes, gas':ab,ti OR 'gas gangrenes':ab,ti OR 'clostridium perfringens':ab,ti OR 'clostridium welchii':ab,ti)	
	#2	('radiotherapy'/exp OR 'radiation therapy'/exp OR 'x ray therapy'/exp OR 'roentgenotherapy'/exp OR 'low dose radiation'/exp OR 'radiotherapy':ab,ti OR 'radiation therapy':ab,ti OR 'radiation therapy, targeted':ab,ti OR 'radiation treatment':ab,ti OR 'radiotherapy, targeted':ab,ti OR 'targeted radiation therapy':ab,ti OR 'targeted radiotherapy':ab,ti OR 'x-ray therapy':ab,ti OR 'x-rays':ab,ti OR 'roentgenotherapy':ab,ti OR 'therapy, x ray':ab,ti OR 'therapy, xray':ab,ti OR 'xray therapy':ab,ti OR 'low dose':ab,ti OR 'low dose radiation':ab,ti OR 'low dose computed tomography':ab,ti OR 'low dose ct':ab,ti)	340,210
	#3	#1 AND #2	187
WOS	#1	**Gas Gangrene** (Abstract) or **Gangrene, Gas** (Abstract) or **Gangrenes, Gas** (Abstract) or **Gas Gangrenes** (Abstract) or **Clostridium perfringens** (Abstract) or **Clostridium welchii** (Abstract)	9,133
	#2	**Radiotherapy** (Abstract) or **Radiation Therapy** (Abstract) or **Radiation Therapy, Targeted** (Abstract) or **Radiation Treatment** (Abstract) or **Radiotherapy, Targeted** (Abstract) or **Targeted Radiation Therapy** (Abstract) or **Targeted Radiotherapy** (Abstract) or **X-Ray Therapy** (Abstract) or **X-Rays** (Abstract) or **Roentgenotherapy** (Abstract) or **Therapy, X Ray** (Abstract) or **Therapy, Xray** (Abstract) or **low dose** (Abstract) or **low dose radiation** (Abstract) or **low dose computed tomography** (Abstract) or **low dose ct** (Abstract)	2,357,176
	#3	#1 AND #2	271
Cochrane Library	#1	("Gas Gangrene":ti,ab,kw OR "Gangrene, Gas":ti,ab,kw OR "Gangrenes, Gas":ti,ab,kw OR "Gas Gangrenes":ti,ab,kw OR "Clostridium perfringens":ti,ab,kw OR "Clostridium welchii":ti,ab,kw)	68
	#2	("Radiotherapy":ti,ab,kw OR "Radiation Therapy":ti,ab,kw OR "Radiation Therapy, Targeted":ti,ab,kw OR "Radiation Treatment":ti,ab,kw OR "Radiotherapy, Targeted":ti,ab,kw OR "Targeted Radiation Therapy":ti,ab,kw OR "Targeted Radiotherapy":ti,ab,kw OR "X-Ray Therapy":ti,ab,kw OR "X-Rays":ti,ab,kw OR "Roentgenotherapy":ti,ab,kw OR "Therapy, X Ray":ti,ab,kw OR "Therapy, Xray":ti,ab,kw OR "Xray Therapy":ti,ab,kw OR "Low Dose":ti,ab,kw OR "Low Dose Radiation":ti,ab,kw OR "Low Dose Computed Tomography":ti,ab,kw OR "Low Dose CT":ti,ab,kw)	1,024
	#3	#1 AND #2	5
Total		Pubmed + Scopus + EMBASE + WOS + Cochrane Library	1,491

DISCUSSION

1.1. Summary of Integrated Findings

The present systematic review synthesized data from six historical studies to evaluate the efficacy of low-dose ionizing radiation (LDIR) as an adjunctive therapy for GG. The integrated findings suggest a substantial survival benefit associated with LDIR, with an overall mortality rate of approximately 11.5% across the pooled cohorts. This represents a marked improvement over the historical control mortality rates of 48–50% cited in the included literature. Furthermore, the review identified a potential limb-sparing effect; patients treated with radiation frequently avoided the extensive therapeutic amputations that were otherwise standard. For instance, subgroup analyses from the Kelly and Dowell series indicated that extremity cases managed with radiation had significantly lower mortality (9.2%) compared to trunk cases (27.5%), and limb salvage was achieved in a

majority of survivors. The timing of intervention emerged as a critical determinant of success, with optimal outcomes observed when irradiation was initiated within 24 to 48 hours of symptom onset. Conversely, the concurrent use of anti-toxin serum appeared to correlate with worse outcomes in some subgroups, suggesting potential antagonistic effects or confounding by indication in more severe cases.

1.2. Comparison of Findings with Past Studies

When contextualizing these historical findings against modern clinical data, the contrast in mortality and morbidity outcomes is striking. Contemporary management of Clostridium perfringens myonecrosis, relying heavily on broad-spectrum antibiotics, aggressive surgical debridement, and hyperbaric oxygen therapy (HBOT), still carries a mortality rate ranging from 20% to 40%, with some reports citing rates as high as 100% in untreated or septic shock cases. While modern aggressive surgery is life-saving, it often necessitates amputation or debilitating tissue loss to achieve source control. In contrast, the historical cohorts reviewed herein suggest that LDIR may have allowed for infection control with less radical surgical intervention, potentially preserving functional limbs. Additionally, recent literature on necrotizing soft tissue infections emphasizes that even with advanced critical care, outcomes remain poor for patients with multiple comorbidities or delayed presentation. The historical mortality rate of 11.5% observed with LDIR is notably lower than these modern benchmarks, raising the question of whether the abandonnement of radiotherapy in the antibiotic era led to the loss of a valuable adjunct that operates through mechanisms distinct from antimicrobial killing, such as immunomodulation (2, 48).

1.3. Strengths and Limitations of the Review

A primary strength of this review is its retrieval and synthesis of overlooked historical data that may have relevance in the emerging era of antimicrobial resistance. By systematically aggregating these early 20th-century reports, the study provides a consolidated evidence base for a therapy that has largely faded from medical memory. However, significant limitations must be acknowledged. The included studies are exclusively observational case series and retrospective reviews from the pre-antibiotic or early sulfonamide era, lacking the rigor of modern randomized controlled trials (RCTs). The absence of standardized dosimetry, variations in radiation voltage (kV) and filtration, and the lack of uniform diagnostic criteria for GG (relying often on clinical crepitus rather than molecular confirmation) introduce substantial heterogeneity. Furthermore, the reliance on historical controls rather than concurrent randomized control groups predisposes the findings to selection bias, where patients selected for radiation might have been less critically ill than those subjected to immediate amputation. Consequently, the reported efficacy estimates must be interpreted with caution.

1.4. Research Gaps

The review highlights critical gaps in the current understanding of host-pathogen interactions under radiation stress. The precise biological mechanism by which LDIR mitigates GG remains unverified; it is unclear whether the observed benefits stemmed from direct bactericidal effects on Clostridium species or, more likely, from the modulation of the host inflammatory response (e.g., reducing the "cytokine storm" or altering leukocyte infiltration). There is a complete absence of modern preclinical in vivo studies using contemporary dosimetry to validate these historical observations. Additionally, no data exists on the efficacy of LDIR against multi-drug resistant strains of Clostridium, representing a significant missed opportunity for alternative therapeutic development. Future research should prioritize animal models to define the optimal therapeutic window and dose-response relationships, followed by safety assessments to determine if LDIR could serve as a viable adjunct in cases where surgical and antibiotic options are exhausted or contraindicated.

CONCLUSION

This systematic review of six historical observational studies suggests that adjunctive low-dose ionizing radiation (LDIR) may have significantly reduced mortality and amputation rates in patients with Clostridium-associated GG compared with contemporaneous standard care, with pooled mortality approximating 11.5% versus historical baselines of 25–50% under surgery and serum therapy alone. Across cohorts, early initiation of LDIR (within 24–48 hours of symptom onset) and repeated fractions appeared to correlate with better survival and limb preservation, particularly in extremity infections, whereas concurrent serum therapy and delayed or limited radiation exposures were associated with worse outcomes. However, these findings derive from non-randomized, methodologically heterogeneous case series lacking standardized dosimetry, modern microbiologic confirmation, or appropriate controls, and are therefore at high risk of bias. In the context of persistently high mortality from GG despite modern antibiotics, surgery, and hyperbaric oxygen, and in view of escalating antimicrobial resistance, these historical data justify renewed preclinical and carefully designed clinical research to clarify mechanisms, define safe and effective dose ranges, and evaluate whether LDIR could be reintroduced as a rigorously tested adjunctive option for severe or refractory clostridial myonecrosis.

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