Infection and Drug Resistance

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CASE REPORT

# Genetic Testing Technology Assisting in the Diagnosis and Treatment of Multiple Suppurative Arthritis and Extensive Migratory Skin and Soft Tissue Infections Caused by Disseminated Staphylococcus aureus Disease: A Case Report and Review

Xiaoyan Hong[1], Yangrong Huang[1], Wei Lin[1], Yi Zhang[1], Jianyun Lin[1], Shengguo Zhang[2], Fengquan Cai[1], Jie Chen[1]

[1]Department of Emergency, Third Affiliated Hospital of Wenzhou Medical University (Rui'an People's Hospital), Wenzhou, Zhejiang, People's Republic of China; [2]Department of Infection, Third Affiliated Hospital of Wenzhou Medical University (Rui'an People's Hospital), Wenzhou, Zhejiang, People's Republic of China

Correspondence: Fengquan Cai; Jie Chen, Department of Emergency, Third Affiliated Hospital of Wenzhou Medical University (Rui'an People's Hospital), 108 Wansong Road, Wenzhou, 325200, Zhejiang, People's Republic of China, Tel +86-13967723666; +86-13587409966, Email cfqruiyi@163.com; woshichenjie@wmu.edu.cn

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**Abstract:** *Staphylococcus aureus (S. aureus)* infection is readily disseminated, yet the multiple septic arthritis and extensive migratory skin and soft tissue infections it causes are uncommon and challenging to treat. The infection can be life-threatening, with a mortality rate of 15–31%. Early, targeted antibiotic therapy is critical to improve prognosis. However, routine cultures are time-consuming and have low positivity rates, which may lead to errors in antibiotic regimen selection, depriving patients of optimal treatment. Genetic testing technologies, such as macrogenomic next-generation sequencing (mNGS) and digital polymerase chain reaction (dPCR), are now emerging as powerful tools for early pathogen diagnosis as well as pathogen diagnosis of target detectors with low microbial loads. In this study, we report a 53-year-old man who was admitted to the ICU for treatment of septic shock. The causative agent was targeted earlier as *S. aureus* by mNGS, and the shock was corrected more quickly with targeted antibiotic medication. However, he later developed multiple septic arthritis and an extensive migratory skin soft tissue infection with persistent fever, and at one point a gram-negative bacterial infection was suspected, and the antibiotic regimen was incorrectly changed. Blood dPCR suggested that the causative organism was still *methicil*lin-*sensitive S. aureus (MSSA)*, with no drug resistance gene detected, and the anti-infective regimen was readjusted, and the patient eventually recovered and was discharged from the hospital. We present this rare case and review related studies to validate the superiority of genetic testing technology in pathogen diagnosis, which deserves further application.

**Keywords:** disseminated *Staphylococcus aureus* disease, multiple suppurative arthritis, extensive migratory skin and soft tissue infections, digital polymerase chain reaction, next-generation sequencing

## Introduction

*S. aureus* is a Gram-positive bacterium widely distributed in nature. Approximately 20% of healthy individuals are persistently colonised with *S. aureus* in their nasopharynx, with the skin, oral cavity, gastrointestinal tract, and lungs serving as secondary sites of colonisation.[1] The study observed that *S. aureus* was the most prevalent bacterial cause of mortality in 135 countries and was also the most common cause of death in individuals aged 15 years and above on

Received: 27 June 2024
Accepted: 12 September 2024
Published: 25 September 2024

a global scale.[2] Pathogenic infections of *S. aureus* have the potential to disseminate and affect nearly every organ system, resulting in *Staphylococcus aureus* disease (DSD). Approximately 70% of cases of pyogenic arthritis are caused by *S. aureus*, with bloodstream dissemination primarily involving single joints. In contrast, multiple pyogenic arthritis remains a rare occurrence.[3,4] The prognosis for multiple pyogenic arthritis associated with DSD is poor, with nearly 50% of affected individuals experiencing irreversible joint damage, resulting in mortality rates as high as 15–31%.[4,5] *S. aureus* is also the most common pathogen causing skin and soft tissue infections, with *S. aureus* skin and soft tissue infections being correlated with a 0.5% increase in the age-standardised mortality rate globally.[6] The combination of multiple pyogenic arthritis, extensive migratory skin and soft tissue infections presents a significant challenge in terms of diagnosis and treatment. Further research is therefore warranted. The surgical and drainage aspects of monoarticular pyogenic arthritis remain a topic of contention, with no consensus yet reached concerning the optimal duration of antibiotic therapy for DSD.[7,8] Pathogen confirmation and monitoring are of great importance in the diagnosis and management of infectious diseases. Early targeted antimicrobial therapy has been shown to improve the prognosis of DSD septic shock patients, while unnecessary antibiotic use has been linked to increased mortality rates.[9–11] Conventional culture remains the gold standard for pathogen diagnosis, but this method has a high rate of false negatives and is time-consuming.[10,11] Furthermore, additional clinically relevant indicators, such as blood tests and imaging, only serve to indirectly reflect the severity or location of infection and are unable to identify the causative pathogen. mNGS has been extensively employed for the early identification of pathogens in critically ill patients, offering an alternative approach to the diagnosis of DSD.[10,12,13] dPCR enables absolute quantification of pathogens, offering superior sensitivity, accuracy, and repeatability. This enables the detection of low pathogen loads and samples showing negative results in conventional cultures.[14,15] However, there is currently a paucity of reports on the application of dPCR in DSD. This study presents a successful case of applying mNGS combined with dPCR for the diagnosis and treatment of multiple pyogenic arthritis and extensive migratory skin and soft tissue infections caused by DSD.

## Case Presentation

The patient, a 53-year-old male with a history of type 2 diabetes mellitus, was admitted to the ICU on July 16, 2023, due to respiratory distress for 12 hours. Three days before admission, the patient complained of swelling and pain in the left palm following trauma. Upon admission, the patient was anuric, with a GCS score of 15, a temperature of 37°C, a respiratory rate of 29 breaths per minute, an average arterial pressure of 65 mmHg (administering epinephrine at 0.4 ug/kg/min), a heart rate of 114 beats per minute, a glycosylated hemoglobin level of 8.03%, mild edema in the extremities, and swelling of the left hand. The wound in the patient's left palm was about 2 by 2cm in diameter and had crusted and healed. Laboratory tests revealed a white blood cell count of $6.6\times10^9$/L, with neutrophils accounting for 86.9%, a highly sensitive C-reactive protein level of 183.16 mg/L, procalcitonin levels of 104.01 ng/mL, lactate levels of 11.5 mmol/L, an oxygenation index of 315 mmHg, creatinine levels of 226 umol/L, bilirubin levels of 29.4 umol/L, and a platelet count of $80\times10^9$/L. The sequential organ failure assessment (SOFA) score was 12, suggesting septic shock as a preliminary diagnosis; the focus and pathogen were still unclear at the time. The patient received adequate fluid resuscitation, continuous renal replacement therapy, intravenous imipenem/cilastatin (0.5g q6h), and intravenous levofloxacin (0.5g qd) for empirical antimicrobial therapy. Three days later, blood mNGS revealed *S. aureus*, with no detected resistance genes, prompting a switch to intravenous cloxacillin (1.5g q6h) for antimicrobial treatment. The patient developed systemic swelling with erythema, and tension blisters appeared on both lower limbs. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was 7. On the 5th day of ICU admission, *MSSA* was isolated from fluid samples from the lower limb blisters and blood cultures. Simultaneously, the patient's average arterial pressure stabilized above 65 mmHg and the SOFA score decreased to 8, and the patient was transferred out of the ICU. There was no intense pain or crepitus in the affected soft-tissue area, and the blisters resolved with simple suction and disinfection, but the patient subsequently exhibited recurrent high fever, with sustained elevation of C-reactive protein levels (Figure 1). On the 9th day, linezolid (0.6g q12h) was added for antimicrobial treatment but the patient showed no improvement. Considering the possibility of concurrent gram-negative bacterial infection, cloxacillin was discontinued, and piperacillin-tazobactam (4.5g q8h) was initiated for antimicrobial therapy, which also resulted in no improvement.

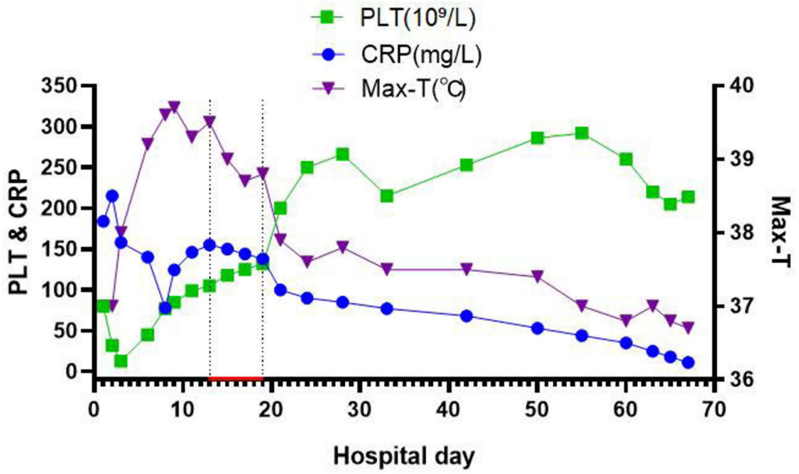


**Figure 1** Changes in the inflammatory factors, blood platelet count, maximum daily body temperature during hospitalization.
**Abbreviations**: CRP, C-reactive protein; PLT, blood platelet; Max-T, maximum body temperature.

Thereafter, fluctuation was palpated in the patient's right ankle, prompting an MRI on the 13th day, which revealed joint effusion (Figure 2B). Ultrasound-guided drainage was performed (Figure 2A), yielding purulent fluid with ++++ white blood cells/high power field (HPF) and 3–5 neutrophils/HPF. Cytology indicated abundant acute inflammatory cells (Figure 2C). However, the recurrent high fever persisted, and cultures of pus, urine, and blood, as well as transthoracic echocardiography, showed negative results multiple times. On the 19th day, blood dPCR was performed, showing a *S. aureus* with a copy number of 1767.5 copies/mL (Figure 3A), confirming *S. aureus* as the causative pathogen. Concurrently, the patient's linezolid blood concentration was 1.08 ug/mL (reference range 2–7 ug/mL), prompting discontinuation of piperacillin-tazobactam and initiation of a combination of linezolid (0.6g q8h) and cloxacillin (1.5g q6h) for antimicrobial therapy. After 8 days of treatment, the linezolid concentration was remeasured at 11.07 ug/mL, and the dosage was adjusted to 0.6g q12h. The patient's systemic swelling resolved, and body temperature remained below 38°C. Dynamic dPCR re-examination showed a decrease in the *S. aureus* copy number, and the positive spots with fluorescent signals were identified (Figure 3A–3C).

On the 27th day of hospitalization, the patient developed swelling and pain in the left knee. MRI revealed joint effusion (Figure 4B), and ultrasound-guided joint drainage was performed (Figure 4A). On the 47th day, the patient developed fluctuating lesions in various areas, including the right shoulder, left hand, right buttock, medial aspect of the right ankle, and left ankle. Incision and drainage were carried out in the right medial ankle and right buttock, yielding hemorrhagic pus. Pus aspiration was performed in other areas using a syringe (Figure 4D–4I). The finger test of the open wound were negative. In addition, further CT, B ultrasound and MRI examinations did not observe the phenomenon of deep soft tissue gas accumulation. On the 48th day, dPCR re-examination yielded a *S. aureus* copy number of 61 copies/mL, leading to the discontinuation of cloxacillin. On the 53rd day, the last blood dPCR showed a *S. aureus* copy number of 32.5 copies/mL. Meanwhile, the drainage tube in the right ankle was removed, allowing the patient to stand. However, an MRI of the left knee revealed osteomyelitis of the left femur (Figure 4C), leading to the placement of a second drainage tube under ultrasound guidance and intra-articular lavage with vancomycin. However, the patient experienced intolerable pain during each lavage, with a numerical rating scale score >7, accompanied by severe limitation of knee joint movement and inability to aspirate joint fluid, prompting cessation of lavage and removal of the lavage drainage tube. Linezolid injection was discontinued on the 57th day, and linezolid tablets (0.6g orally q12h) were initiated for treatment. The patient remained afebrile after 60 days. On the 67th day, the patient was able to walk independently with one drainage tube in the left knee, and was discharged. Ten days later, all antimicrobial agents were discontinued, and the drainage tube in the left knee was removed, allowing slow independent walking and recovery to baseline. His clinical course is presented in Figure 5.

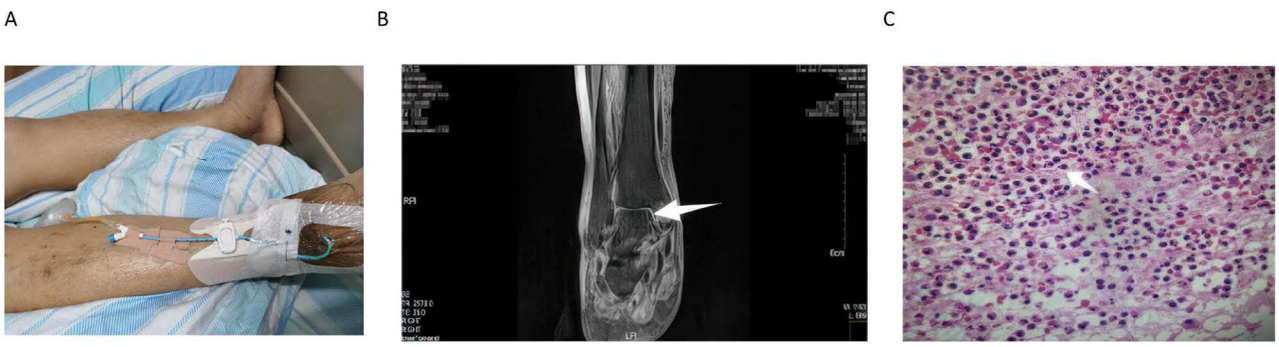


**Figure 2** Examination and treatment of right ankle. Panel (**A**) Ultrasound-guided catheter drainage for purulent arthritis of the right ankle on day 13. Panel (**B**) Right ankle MR images on the 13th day. Panel (**C**) Cytology of the right ankle joint fluid.

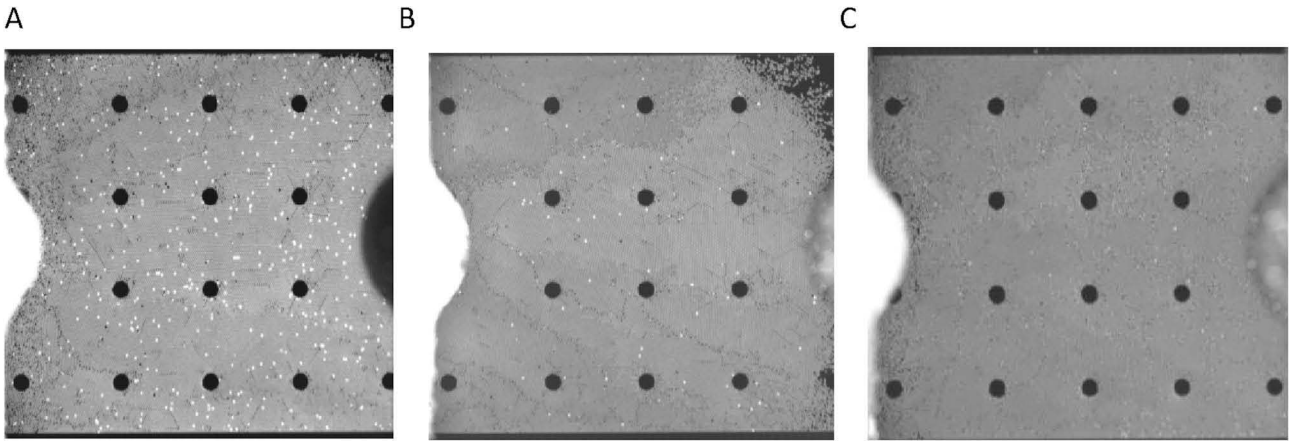


**Figure 3** Absolute quantification of staphylococcus aureus concentration in patient plasma using dPCR. Panel (**A**) Patient blood dPCR microarray on day 19 of hospitalization. Panel (**B**) Patient blood dPCR microarray on 29th day. Panel (**C**) Patient blood dPCR microarray on 48th day.

## Discussion

*S. aureus*-induced bloodstream infections have the potential to disseminate to various parts of the body with ease. DSD is typified by symptoms including fever, persistent bacteremia, and involvement of two or more distinct tissue sites, commonly affecting organs such as the joints, skin, heart, and central nervous system.[4] It is well established that diabetes mellitus represents a significant predisposing factor for disseminated infections caused by *S. aureus*. In many cases, minor wounds serve as potential sources of these infections.[3] In this case, the initial focus of infection in the patient is likely to be the trauma site on the left hand. Inadequate wound care permitted the pathogen to disseminate through the bloodstream, resulting in the involvement of the skin, soft tissues, joint spaces, and bone marrow throughout the body. Hematogenous spread represents the primary route of infection in pyogenic arthritis, predominantly affecting joints such as the shoulder, knee, wrist, and elbow. The majority of cases of pyogenic arthritis involve a single joint, with only 5% to 10% affecting multiple joints.[3,4]

Flucloxacillin or cloxacillin is the recommended treatment for infections of the bloodstream caused by *MSSA*. However, in cases of dissemination, the required dosage often exceeds standard recommendations, leading to a preference for intermittent dosing combined with continuous infusion via a micro-pump.[16] The utilisation of an off-label pharmaceutical agent may precipitate adverse reactions, and the deployment of a micro-pump infusion may impede the rehabilitation process. In this instance, the patient was treated with the maximum recommended dose of cloxacillin and underwent drainage of the affected lesions, yet recurrent fever persisted. It has been demonstrated that the standard doses of flucloxacillin are insufficient to achieve the desired therapeutic concentrations in the skin, soft tissue, and joints.[17] Both flucloxacillin and cloxacillin exhibit comparable pharmacokinetics and dosing regimens.[18] It is postulated that the primary

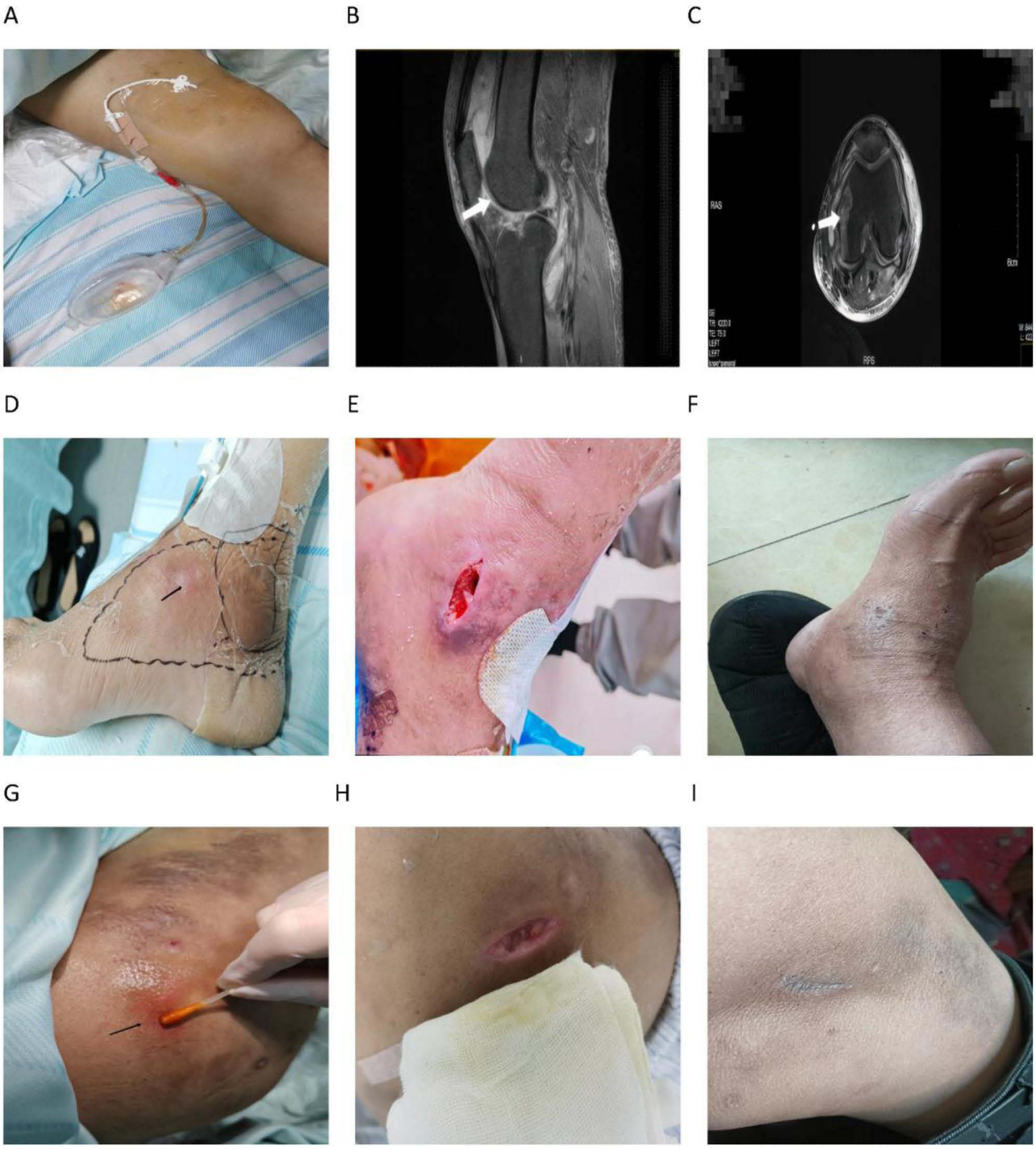


**Figure 4** Treatment and MR images of left knee, as well as incision and drainage of multiple skin and soft tissue infections. Panel (**A**) Ultrasound-guided catheter drainage for purulent arthritis of the left knee on day 27. Panel (**B**) and **C**) Left knee MR images on the 27th day and on the 53rd day, respectively. Panel (**D**)**–(F**) The process of incision and drainage of right ankle infection until healing. Panel (**G**)**–(I**)The process of incision and drainage of right buttock infection until healing.

reason for the lack of efficacy of cloxacillin was insufficient tissue concentrations. In contrast, linezolid demonstrates high tissue permeability to skin, soft tissue, bone, and joints, independent of tissue perfusion.[19,20] Consequently, an anti-infective regimen including linezolid was adopted and plasma concentrations were monitored to guide dose adjustments, with the objective of improving treatment success rates and minimising adverse drug reactions.[21] In this case, the patient exhibited a low blood concentration of linezolid during significant soft tissue swelling, prompting us to increase the dosage to 0.6

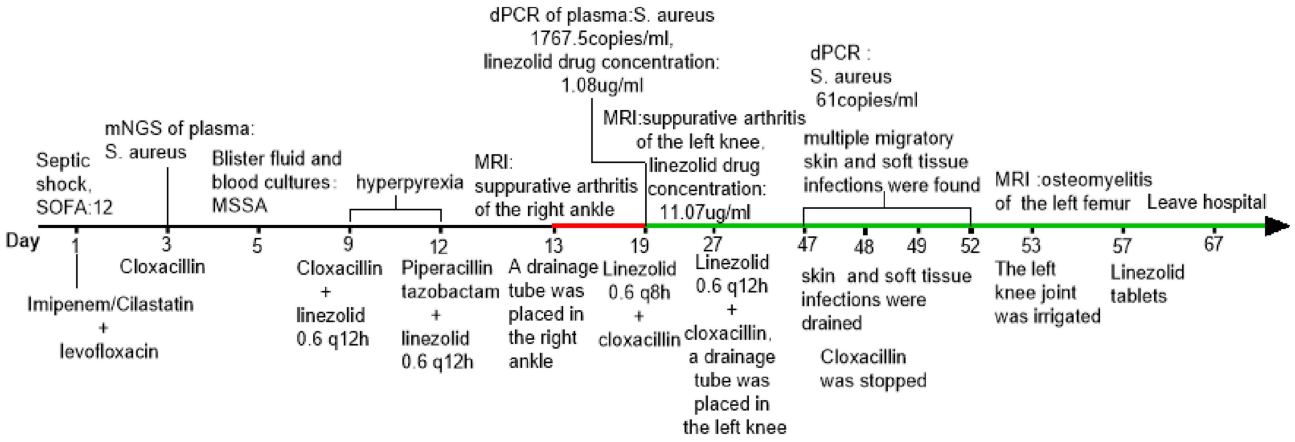


**Figure 5** The course of the patient's hospitalization.

g every 8 hours. Continuous monitoring of linezolid blood concentrations revealed decreasing drug requirements as the patient's condition improved and swelling decreased. Despite the patient's prolonged illness, adverse reactions to linezolid, such as thrombocytopenia, anemia, and gastrointestinal symptoms, were not evident.

The optimal duration of antibiotic therapy for DSD remains undetermined, but therapy typically lasts no less than 4 weeks for complex infections.[8] Oon, Zhi Sing et al reported a case of a 12-year-old male with an *MSSA* infection resulting in a thigh abscess, pyogenic arthritis of the ankle joint, and osteomyelitis; the patient recovered after 10 weeks of antibiotic therapy.[22] Due to the patient's multiple pyogenic arthritis and osteomyelitis sites with extensive skin and soft tissue infections, antibiotic therapy was extended to 11 weeks, comprising intravenous and oral antibiotics.

Complex skin and soft tissue infections are mostly treated with a combination of antibiotics and surgical debridement.[23] In this case, the patient had extensive, recurrent skin and soft tissue infections and persistent fever despite the antibiotic treatment. Necrotizing fasciitis was a concern, but difficult to distinguish accurately in the early stage.[24] However, the patient's shock quickly corrected, the blister did not expand after simple aspiration, and subsequent ultrasonography, CT, MRI, and finger test did not support the diagnosis of necrotizing fasciitis. Considering the impracticality of performing surgical debridement in all affected areas, local incision and drainage were performed at the larger areas of the right buttock and medial right ankle. For smaller infected areas, direct aspiration with a syringe was carried out. These methods provided adequate drainage of the lesions while minimizing patient harm.

The main treatment methods for purulent arthritis include antibiotics and joint surgery or drainage. The optimal approach to joint surgery and drainage remain controversial, with the primary modalities including open joint incision, arthroscopic examination, and joint puncture.[6] Doub, James B et al have successfully treated patients with purulent arthritis due to disseminated *S. aureus* using conservative antibiotic therapy alone.[25] However, the aforementioned cases involved single instances of purulent arthritis, whereas the patient in this case presented with multiple purulent arthritis episodes, affecting the knee joint and ankle joint, and extending to the bone marrow, accompanied by recurrent fever. Therefore, in addition to antibiotic treatment, the patient underwent ultrasound-guided catheter drainage of the right ankle and left knee joints. Studies have shown that intra-articular injection of vancomycin into the knee joint cavity can increase local antibiotic concentration, effectively treating periprosthetic joint infections.[26] A few scholars have mentioned its use in natural joints, the intra-articular antibiotic injections may lead to an increase in vancomycin resistance, and local joint injections are not approved and are off-label.[27] In addition, the intra-articular antibiotic injections were not tolerable for the patient; hence, this treatment plan was terminated after only two washouts. Therefore, the injection of vancomycin in native joints needs to be done with caution.

A review of the literature was conducted on the application of novel genetic detection technologies, including mNGS and dPCR, in the diagnosis and treatment of DSD.

A case report demonstrated the application of mNGS in the diagnosis and treatment of progressive severe pneumonia and septic shock caused by *S. aureus*.[12] Furthermore, a comparative study has demonstrated the efficacy of mNGS in the

detection of pathogens in invasive bone and joint infections, with *S. aureus* being the most frequently identified pathogen, predominantly originating from invasive procedures that result in bloodstream dissemination.[13] As a high-throughput sequencing technique, mNGS has broad coverage, which increases the detection rate of pathogens and shortens the detection time. The results are available as early as 24–78 hours, offering significantly faster results than those obtained through conventional cultures. Consequently, this technique is appropriate for the preliminary identification of infection in patients with unidentified pathogens, thereby facilitating the prompt initiation of targeted antibiotic therapy.[10] In the present case, mNGS testing was conducted on the second day of hospitalization, with results becoming available on the third day. This enabled the adjustment of antibiotic therapy. Subsequent blister fluid and blood cultures confirmed the mNGS results. Compared to the other two methods, mNGS provided results 24–48 hours earlier.

Nevertheless, mNGS is expensive, lacks standardised operational procedures and criteria for pathogen diagnosis, and displays significant inter-laboratory inconsistencies, thereby limiting its comparability. The results obtained can only provide a rough identification of microbial species and an estimation of their approximate proportions.[28] Polymerase Chain Reaction (PCR) is a molecular biology technique that amplifies specific DNA fragments and has been employed for over 30 years. Currently, third-generation dPCR has been developed. Compared to traditional PCR, dPCR does not require standards or standard curve preparation. This single-molecule amplification technique offers absolute quantification with higher sensitivity, accuracy, and repeatability.[14,29] A droplet dPCR assay algorithm was employed, whereby a patient's blood sample was subjected to centrifugation to obtain plasma, followed by the extraction of circulating free DNA (cfDNA). Once the detection system was configured, it was partitioned into tens of thousands of small water-in-oil droplets using a droplet preparation instrument, which were subsequently stored on a chip. Following the PCR amplification process, the droplets that contained the target fragment were in turn exposed to specific primers and probes, which resulted in the emission of fluorescence. The reading analyser quantified the concentration of the target fragment by calculating the total number of droplets and the number of negative droplets using the Poisson distribution, thereby achieving absolute quantification.

Due to its high precision and sensitivity in detecting samples with low virus and tumour cell loads, dPCR has been widely used in virus detection and oncology.[14,15,29,30] Furthermore, a number of targets have been developed in the field of bacterial detection, with the technique becoming increasingly applied in food safety management and clinical practice in recent years.[14] Despite the dearth of reports and studies on the utilisation of dPCR in DSD patients, research conducted by Yu Li et al has illustrated the efficacy of dPCR in sepsis. This research has demonstrated that dPCR can detect the pathogenic microorganisms in sepsis patients at an earlier and more accurate stage than blood cultures and traditional PCR. Furthermore, dPCR has the capacity to yield positive results in culture-negative specimens.[11] This suggests that dPCR is also capable of detecting low bacterial concentrations. In the initial presentation, the patient exhibited recurrent high fever, with a suspected concurrent Gram-negative bacterial infection. However, the cultures of pus and blood specimens yielded negative results, posing a challenge for the treatment plan. The patient had undergone multiple antibiotic treatments previously, which suggests the possibility of a low pathogen load in the body. Accordingly, dPCR was selected as the pathogen detection method. The dPCR method has the capacity to detect 18 distinct types of hospital-acquired infection pathogens, including *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Acinetobacter baumannii, Streptococcus pneumoniae, Enterococcus, Streptococcus, and Coagulase-negative Staphylococcus*. Additionally, it can identify five common drug-resistant genes, namely *Bia KPC, Meca, Bla OXA-48, Bla NDM/Bla IMP*, and *Van A/VanM*. Of these, *Meca* is a methicillin-resistant staphylococcus-specific resistance gene. According to the hospital's acquired infection pathogens species statistics, this test covers all common relevant pathogens. The dPCR results confirmed that the pathogen was *S. aureus*, which guided the selection of an appropriate antimicrobial therapy regimen along with drainage, resulting in the gradual normalization of the patient's body temperature. This also demonstrates that dPCR is an excellent validation tool for mNGS.

To date, no studies or reports have indicated that the copy number of *S. aureus* can be monitored by dPCR to assess the severity of infection. However, dPCR has been successfully applied in the dynamic monitoring of pathogen load to evaluate disease severity and treatment efficacy in populations with Ebola virus infection[31] and Chlamydia pneumoniae infection.[32] During the course of the patient's hospitalisation, blood dPCR was performed on multiple occasions, demonstrating a gradual reduction in the copy number of *S. aureus* and suggesting an improvement in the patient's

condition. The quantitative results reflect the load of *S. aureus* in the blood, which is closely correlated with disease severity and treatment efficacy. At 48 days, blood dPCR revealed a *S. aureus* copy number of 61 copies/mL, indicating that the infections in the joint cavity, skin and soft tissues, and bone marrow remained uncontrolled. Nevertheless, the cloxacillin injections were terminated. At 53 days, the final blood dPCR indicated a further reduction in bacterial copy number, accompanied by a continued improvement in the patient's symptoms. It is therefore important to consider the timing of the reduction and discontinuation of antibiotics. It is regrettable that no pertinent studies have examined the utility of dPCR monitoring of pathogen load in guiding antibiotic therapy.

## Conclusions

The mNGS technique has the potential to facilitate the earlier identification of pathogenic bacteria than conventional culture techniques. This has the advantage of enabling the implementation of early antibiotic-targeted therapy. Furthermore, in instances where the pathogen load is low following antibiotic treatment, the utilisation of dPCR technology enhances the positive detection rate of the causative organisms and facilitates the guidance of the antibiotic regimen. The aforementioned genetic testing techniques, which played an instrumental role in the treatment of our patient with DSD, contributed to the patient's recovery. The findings of our study may also inform the management of other patients with severe infections of unknown aetiology. However, it is important to acknowledge the limitations of mNGS and dPCR. mNGS provides an estimate of the number of sequences, which may not accurately reflect the absolute abundance of pathogenic microorganisms. Furthermore, the monitoring of pathogen copy number by dPCR to inform antibiotic stewardship remains a developing area of research.

## Abbreviations

dPCR, digital polymerase chain reaction; DSD, disseminated *staphylococcus aureus* disease; mNGS, metagenomic next-generation sequencing; *MSSA, methicillin-sensitive Staphylococcus aureus*; PCR, polymerase chain reaction; *S. aureus, Staphylococcus aureus*; SOFA, Sequential organ failure assessment; HPF, high power field; INEC, Laboratory Risk Indicator for Necrotizing Fasciitis; cfDNA, circulating free DNA.

## Ethics Approval and Consent to Participate

The study protocol and publication of the case details were approved by the Institutional Review Board of the Third Affiliated Hospital of Wenzhou Medical University. Consent for publication: Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

## Acknowledgments

The authors wish to thank the patient for participating in this study. We also thank Dr. Liang Hong and Dr. Zhan-wei Ruan for their help in the case discussion.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

Higher education teaching reform project of Wenzhou medical university (NO JG2023072).

## Disclosure

All authors declare no potential conflicts of interest relevant to this article.

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