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Posted Date: 14 October 2025

doi: 10.20944/preprints202510.1023.v1

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Review

Molecular Epidemiology Clinical Manifestations, Decolonization Strategies and Treatment Options of Methicillin-Susceptible *Staphylococcus aureus* Infection in Neonates

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Abstract

Methicillin-sensitive *Staphylococcus aureus* (MSSA) infection continues to be a significant public health issue in neonatal intensive care units (NICUs). Although the research mostly focuses on methicillin-resistant *Staphylococcus aureus* (MRSA), new data reveal that methicillin-sensitive *Staphylococcus aureus* (MSSA) infections are three to four times more prevalent in neonates, correlating with increased mortality and morbidity. This study analyzes the molecular attributes, epidemiology, risk factors, clinical presentations, decontamination methods, and treatment alternatives for MSSA infections in newborns. Results demonstrate that MSSA strains possess considerable genetic diversity, as they are distinguished by a wide variety of sequence types (STs) and Staphylococcal Protein A types (SpA) and harbor several pathogenicity genes, including hemolysins and superantigens, which are implicated in severe infections, such as necrotizing pneumonia in PVL-positive strains. The epidemiological load is still high over the globe, and more newborns, parents, and healthcare workers are being colonized. Prematurity, low birth weight, lengthy hospitalization and the use of intrusive technologies are some of the biggest risk factors. Clinical signs include skin and soft tissue infections, bacteremia, and sepsis, with severe consequences such as endocarditis. Decolonization procedures using mupirocin and chlorhexidine have shown efficacy, but constrained by escalating resistance. In terms of treatment, β -lactams are still the best option. Cefazolin and isoxazolympenicillins work better than vancomycin in clinical results. For a limited time, they may also be used with aminoglycosides for severe infections. In conclusion, MSSA infections in newborns are as perilous as MRSA, necessitating enhanced monitoring, the implementation of focused prevention strategies, and the development of novel treatment methods to mitigate morbidity and death in this susceptible population.

Keywords: MSSA; infection; neonates; NICU; resistance; antibiotics; treatment

1. Introduction

Soon after completing his undergraduate education at the University of Aberdeen in Scotland, Alexander Ogston first described *Staphylococcus* in 1880, a Gram-positive spherical “micrococci,” named after the Greek term for “bunches of grapes” [1].

Staphylococcus aureus [2] is a common infection acquired both in hospitals and the community. It causes a lot of different diseases in people, from mild skin and soft tissue infections to serious and even deadly ones [3].

In 1961, the United Kingdom reported *S. aureus* isolates that had developed resistance to methicillin (methicillin-resistant *S. aureus*, MRSA). Additionally, the term MSSA was introduced in

order to describe *S. aureus* strains that remain still susceptible to methicillin and other beta-lactam antibiotics [4].

The prevalence of *S. aureus* strains associated with human infections has significantly escalated worldwide, particularly for methicillin-susceptible *Staphylococcus aureus* (MSSA), despite the epidemiology of *S. aureus* strain diversity showing regional variations [5–7]. MSSA is becoming a serious burden for public health [1, 8].

More specifically, despite the increasing occurrence of MRSA infections, methicillin-sensitive *S. aureus* (MSSA) infections remain approximately 3 to 4 times more prevalent among neonates in the NICU [9,10] and neonates, which could be even more significant regarding neonatal morbidity and mortality [9,10,11,12].

There is strong evidence that virulence genes may play a role in severe MSSA infections, which are exacerbated worse by the spread of drug-resistant strains and their widespread circulation [5].

Numerous publications have provided epidemiological information on neonatal MSSA following the implementation of surveillance measures, transmission control, and decolonization strategies. While the overall rate of invasive *S. aureus* infections increased over the past 20 years, because of the increase in the number of MRSA infections, MSSA infections were significantly reduced at about 23 per 10,000 hospitalized neonates, but remained more common than MRSA infections regardless of birth weight and with similar mortality rates [10].

Taking the aforementioned into consideration the objective of the present paper is to review the current evidence and offer new perspectives on the molecular features, epidemiology, risk factors, clinical symptoms, decolonization techniques and therapeutic approaches for MSSA infection in neonates.

For this reason, in July and August 2025, two researchers conducted independently a literature search on Pubmed, Google scholar and Scopus databases to construct a narrative review. Only studies involving humans and articles in English were taken into account. The phrases 'Methicillin-sensitive *Staphylococcus aureus*' OR 'MSSA' AND 'neonate' OR 'newborn' OR 'infant' OR 'Neonatal Intensive Care Unit' OR 'Neonatology' were employed. The studies that were selected were assessed based on their titles, abstracts and relevance to this narrative review. We retrieved 485 articles, 68 of them were found to be relevant.

2. Molecular Epidemiology of MSSA

2.1. Molecular Characteristics of MSSA

An examination of MSSA's molecular attributes may clarify its origin, colonization methods and possible evolution into resistant strains.

One of the most important things that molecular research has shown is that MSSA strains have a lot of genetic diversity. MSSA is distinguished by a wide variety of sequence types (STs) and Staphylococcal Protein A types (SpA), while MRSA often exhibits a restricted number of dominant clonal types as a result of the spread of certain epidemic strains. There may be many different clones in different areas and research organizations, however studies using multilocus sequence typing (MLST) have indicated that ST398 and ST15 are two of the most common STs in MSSA [13]. This vast spectrum of features shows how MSSA has altered to live in many various places, including the human body.

MSSA strains have a variety of genes that make them resistant to a lot of different antimicrobials, even if they are poor against methicillin. The *blaZ* gene, which codes for a β -lactamase, is the most common one and is identified in more than 85–90% of isolates. This gene is what renders MSSA strains resistant to penicillin, which is thought to be almost everywhere right now [14].

Tet(K), which is connected to an efflux pump for tetracyclines, and *erm*(C), which makes cells resistant to macrolides by methylating the 23S rRNA, are also present at this time. These genes show that MSSA are not "innocent" when it comes to resistance, even if they have lower rates. They could also be a source of genes that can be passed on to other strains or species.

It is also extremely crucial to look at the pathogenic profile of MSSA. Most isolates feature genes that code for hemolysins, such as *hla*, *hld*, *hlgA*, *hlgB*, and *hlgC*. These genes contribute to break down host cells and propagate the infection [15]. In addition to these toxins, recognized virulence factors such as enterotoxins and superantigens may have novel functions, particularly in eliciting proinflammatory responses in airway epithelium, thereby enhancing the inflammatory milieu during infection [15].

The Panton–Valentine leukocyte toxin (*pvl*) gene is seldom present in MSSA, differentiating them from some pandemic MRSA strains where PVL is often detected and linked to severe cutaneous and pulmonary infections [16]. These strains have different virulence factors, including surface adhesion proteins (MSCRAMMs), toxic shock syndrome toxins (TSST-1) and enterotoxins. These factors may cause serious problems in those who are vulnerable. Thus, the lack or rarity of *pvl* does not lessen the pathogenic importance of MSSA.

The immune evasion cluster (IEC) is another key part of MSSA. It includes genes like *sak* (staphylokinase), *chp* (chemotaxis inhibitory protein) and *scn* (staphylococcal complement inhibitor). IEC gives MSSA strains an edge over the immune system by inhibiting the activation of complement, the migration of neutrophils and the breakdown of fibrin [17]. The idea that MSSA strains have evolved strong ways to avoid the immune system, which makes it easier for them to stay in one place and spread, is supported by the fact that IEC is present in a large number of isolates.

Molecular characteristics and the clinical behavior of MSSA are interconnected in a complex manner. Varied strains may have varied degrees of virulence and susceptibility because of genetic variations. MSSA uses surface adhesion proteins and immune evasion factors to colonize the nasopharyngeal and cutaneous epithelium in newborns and babies, which is when their immune systems are still developing. This makes the environment more likely to be infected [18]. This is why MSSA infections in newborns may be equally as dangerous as MRSA infections, even if the germs aren't resistant to methicillin. They may lead to pneumonia, sepsis, or endocarditis. Additionally, MSSA strains seem to serve as a possible "hotbed" for the generation of novel MRSA clones. Mobile genetic elements like plasmids, transposons and phages may pass on resistance genes like *mecA* or *mecC* that render bacteria resistant to methicillin [19]. Consequently, molecular monitoring of MRSA is vital for forecasting the development of novel MRSA strains with potentially higher virulence and for comprehending the existing epidemiological landscape. Lastly, MSSA contains a number of distinct genes, thus various clones may be more frequent in different hospitals or places. This might lead to varied clinical consequences. For instance, studies have shown that ST398 is more frequent in Asia, whereas ST15 and ST30 are more common in North America and Europe [20]. This variety demands ongoing molecular typing and documentation to promptly identify strains capable of fast diffusion or exhibiting very harmful virulence profiles. In general, the molecular traits of MSSA show that it is a very flexible organism with many other pathogenicity factors and resistance strategies than methicillin. To formulate focused control and preventive methods, particularly for high-risk neonatal groups, it is essential to understand the genetic structure, resistance genes, and toxic components of MSSA. To get a more profound understanding of the function of MSSA in newborn infections, more study is necessary, focusing on polyclonal analysis, genomic monitoring and connection with clinical data.

2.2. Antimicrobial Resistance

One of the most hazardous bacteria that afflict people is *Staphylococcus aureus*. It may lead to a variety of infections, ranging from modest skin issues to severe and sometimes fatal conditions such as endocarditis, pneumonia, and bacteremia. Methicillin-susceptible strains (MSSA) are as significant as methicillin-resistant strains (MRSA), which have rightfully received the majority of clinical and scientific attention. Their antimicrobial resistance profile, on the other hand, has unique characteristics that need to be studied extensively because they impact treatment plans and patient outcomes, particularly in neonatal critical care units where there aren't many other options for antibiotics.

The term "MSSA" makes it seem like these bacteria are resistant to methicillin and other β -lactams that are resistant to penicillinase's action. However, most MSSA strains are not resistant to basic penicillin. The main way this happens is via the *blaZ* gene, which makes a penicillinase that can break down penicillin G and other related chemicals. Penicillin is not an appropriate choice for empirical or targeted treatment of MSSA infections, since resistance occurs in about 80–90% of MSSA isolates [14]. So, clinicians use other β -lactams that still function, including isoxazolympenicillins (oxacillin and nafcillin) or first-generation cephalosporins (cefazolin).

In addition to penicillin, MSSA strains typically carry genes that make them resistant to other kinds of antibiotics. For example, the *erm* genes, which code for 23S rRNA methylases like *erm(A)* and *erm(C)*, are a frequent example. These enzymes change the binding sites of streptogramin B, lincosamides, and macrolides, which gives them an MLSB resistance phenotype. Medicines like erythromycin and clindamycin, which are typically administered to children and infants, don't function as effectively when these genes exist in MSSA from both hospitals and the community. This is because they are extremely tolerant and as a result has clinical consequences [21, 22].

The *tet(K)* and *tet(M)* genes are the most important ones that make MSSA strains resistant to tetracycline. *Tet(K)* codes for a pump that moves things out of cells, whereas *tet(M)* codes for a mechanism to protect ribosomes. Tetracyclines are still used to treat skin and soft tissue infections in certain circumstances, although they don't function as effectively because of both *tet(K)* and *tet(M)*, as being supported by Roberts [23]. Scientists have found these genes in MSSA strains from a number of different nations. This means that MSSA strains are not "innocent" and may have strategies to spread resistance. It is especially interesting that fusidic acid, an antibiotic that is often used both topically and systemically in many nations, is not effective anymore. MSSA strains have resistance to fusidic acid, which is primarily due to changes in the *fusA* gene, which codes for the protein synthesis elongation factor G (EF-G), or the existence of the *fusB* and *fusC* genes, which protect EF-G [24]. This is significant for therapy since fusidic acid is often used to treat infections in neonates and in pediatric dermatology. Mupirocin resistance is another major category. Mupirocin is a topical antibiotic that is widely used to get rid of nasal *Staphylococcus aureus*, which helps stop infections in critical care settings. Bacteria may develop resistance to mupirocin in two ways: point mutations in the *ileS* gene, which codes for isoleucyl-tRNA synthetase, induce low-level resistance and acquiring the *mupA* gene causes high-level resistance [25]. It is especially worrying since MSSA strains that are resistant to mupirocin are becoming more common in places like intensive care units (ICUs), where decolonization is an important way to stop the spread of infections.

MSSA may potentially develop resistance to aminoglycosides, such as gentamicin, via genes that code for enzymes that alter aminoglycosides (*AAC*, *ANT*, and *APH*). Aminoglycosides and β -lactam antibiotics are used combined to treat severe infections. Resistance may be clinically significant, despite the general perception that MSSA is more susceptible to these medications than MRSA [26]. It is also important to remember that MSSA might become less sensitive via adaptive mechanisms, even if it usually still responds to glycopeptides (vancomycin, teicoplanin) and newer antistaphylococcal antibiotics (linezolid, daptomycin). These pathways result in the emergence of "vancomycin-intermediate *S. aureus*" (VISA) phenotypes, distinguished by cell wall thickening, increased D-alanine synthesis, and modifications in penicillin-binding proteins (PBPs). There have been a few cases like this in MSSA, which suggests that even "susceptible" strains may alter in scary ways when exposed to antibiotics.

MSSA antibiotic resistance is a concern for public health and medicine. Other types of *S. aureus*, including MRSA, may acquire resistance genes from MSSA strains via mobile genetic elements like plasmids, transposons, and phages. So, it's crucial to keep an eye on MSSA resistance to halt the formation of new resistant clones that may spread like an epidemic and to make sure that therapy works [19].

3. Epidemiology of MSSA Burden

The epidemiology of *Staphylococcus aureus*, especially methicillin-susceptible strains (MSSA), in neonatal intensive care units (NICUs) is a crucial field of research, given that newborns represent a particularly sensitive population at heightened risk of infection. Even in regions where infection control measures have considerably cut down on the number of MRSA cases, MSSA is still a major cause of infections in hospitals and in the community [27]. As a result, MSSA remains a common infection in NICUs, leading to significant morbidity and mortality.

One of the most essential things to remember about the last few decades is that MSSA infections in infants are still three to four times more common than MRSA infections, even in locations where resistant strains are common [22]. This impact is most noticeable in bloodstream infections, where MSSA is still responsible for many cases of sepsis in NICUs. The elevated prevalence of MSSA colonization in the nasal mucosa of neonates and healthcare personnel constitutes a significant transmission vector, with 20–30% of the general population harboring MSSA in the nasopharynx asymptotically [28].

The death rate linked to MSSA in NICUs is similar to that of MRSA. Research indicates that whereas MRSA infections often exhibit heightened resistance to treatment, the rates of complications and mortality do not substantially vary between MSSA and MRSA in newborns [27]. This shows that being susceptible to methicillin doesn't always mean that the clinical picture is less severe, as MSSA has a wide range of virulent agents.

The geographical distribution and temporal patterns are noteworthy. In Europe and the United States, improved infection control measures, including rigorous hand hygiene, surveillance cultures and decolonization protocols, have resulted in a reduction of MRSA cases. However, the overall incidence of *S. aureus* infections has remained constant, attributed to the prevalence of MSSA [29]. Conversely, in Asian nations with elevated MRSA prevalence, MSSA persists as a notable pathogen, particularly in skin and soft tissue infections, as well as in sepsis [13].

The profile of MSSA infections related to birth weight and prematurity is particularly significant. Premature and low birth weight infants have an increased susceptibility to colonization and infection, due to their immature immune systems and the need for prolonged hospitalization and medical treatments (such as intravenous catheters and mechanical ventilation). Studies show that MSSA infections in certain groups may have very bad effects, similar to those of MRSA [30].

Epidemiological surveillance studies have shown that the implementation of preventive and control measures, such as carrier isolation, the adoption of decontamination protocols and strict adherence to aseptic standards, leads to a significant reduction in MSSA infections. For example, a study done in the United States found that systematic surveillance and decontamination with mupirocin and chlorhexidine cut the number of MSSA infections in NICUs by half [29]. European studies indicate that regular screening and environmental disinfection reduce the transmission of MSSA from healthcare professionals to newborns [31].

An important point is that the epidemiology of MSSA in NICUs includes not only newborns who are in the hospital, but also their parents and healthcare workers. Recent studies show that MSSA isolates from parents and healthcare workers typically have genetic similarities to those from babies. This suggests that there are ways for the bacteria to spread inside the NICU [27]. This knowledge is necessary for developing control methods that include both neonates and their surrounding environment.

In general, the epidemiology of MSSA in NICUs demonstrates that it is still as important in the clinic and in the field as MRSA. MSSA is a major priority for monitoring and care since it is becoming more common, the symptoms are becoming worse and asymptomatic carriers may spread it. To limit the transmission of illness, people should focus on discovering carriers, observing strict cleaning norms, and employing decontamination methods when necessary. It is crucial to know how MSSA spreads in various parts of the globe so that newborns don't become ill or die.

4. Risk Factors and Clinical Manifestations of MSSA Infection in Neonates

4.1. Colonization

According to Otokunefor[32] there has been analysis for 19 PVL-MSSA clinical isolates obtained from the Nottingham University Hospitals NHS Trust (NUHT) microbiology laboratory, selected due to clinical suspicion or an antibiogram indicating gentamicin/trimethoprim resistance associated with PVL positive. The Health Protection Agency's national Staphylococcus Reference Unit (SRU) then tested these isolates for PVL. There were two clusters: TS6 and TS9 were taken from different patients on the same hospital ward, TS18 and TS24 were taken from different samples of an unrelated patient, and TS17 was taken from a relative of this patient. The isolates came from a variety of sample types, clinical histories, and patient ages (Table 1) and did not have any known epidemiological links. As previously described [33, 34], multiplex PCRs were used to check for the presence or absence of 13 toxin genes (sea, seb, sec, sed, saw, seg, seh, sei, sej, tst, eta, etb, and etd) in this group. The isolates were genotyping via spa typing and sequence-based multilocus sequence typing (MLST). After sequencing the variable X region of the spa gene as previously described [35], all isolates were spa typed using the Ridom GmbH spa website, www.spaserver.ridom.de, and multilocus sequence types were mapped using the spa <http://spa.ridom.de/mlst.shtml> database. The *S. aureus* database, <http://saureus.mlst.net/>, was used with MLST [36] to provide further characterization of representative isolates. To find out what sort of PVL it was, primers LukSF (ATGGTCAAAAAGACTATTAGCTG), LukSR (TCAAATTCACCTGTATCTCCTGAG), LukFF (TCAGTAAACGTTGTAGATTATGCACC), and LukFR (nATTTTCATCTTTATAATTATTACCTATC) were used to amplify and sequence two internal segments of 764 bp and 535 bp in the lukS and lukF loci, respectively. Nine PCRs [37, 38] were used to ascertain particular PVL-encoding phage types. These PCRs found six PVL-encoding phages (Table 2) and PVL phages that weren't well known but were either icosahedral or elongated head types.

Table 1. Resistance according to Genes.

Gene	Mechanism / Function	Clinicalrelevance	Reference
blaZ	Encodes β-lactamase hydrolyzing penicillin G and other natural β-lactams	Widespread resistance to penicillin (>80–90% of MSSA isolates)	Becker et al., 2014
erm(A), erm(C)	23S rRNA methylation → MLSB phenotype (resistance to macrolides, lincosamides, streptogramin B)	Reduced efficacy of clindamycin and erythromycin in neonatal isolates	Leclercq, 2002
tet(K), tet(M)	Efflux pump (tetK) or ribosomal protection protein (tetM) → tetracycline resistance	Limited clinical utility of tetracyclines in SSTIs	Roberts, 2005
fusB, fusC, fusAmut.	Protection or modification of EF-G → fusidic acid resistance	Clinically relevant resistance in regions with extensive topical fusidic acid use	O'Neill&Chopra, 2006
mupA, mupB, ileSmut.	Modification of isoleucyl-tRNA synthetase → mupirocin resistance	Reduces effectiveness of mupirocin-based decolonization strategies	Patel et al., 2009

Gene	Mechanism / Function	Clinicalrelevance	Reference
aac, ant, aph	Aminoglycoside-modifying enzymes (acetyltransferases, phosphotransferases, nucleotidyltransferases)	Resistance to gentamicin and other aminoglycosides, limits synergistic use with β -lactams	Chandrakanth et al., 2008

Table 2. Measures to prevent MSSA colonization.

Bacterial presence in the throat and nasal passages	Positioning the newborn on the mother's breast immediately after birth. Precolonization of the typical α - and/or A -Streptococcus by applying the mother's breast milk over and inside the mouths of extremely-low-birth-weight infants immediately upon their admission to the NICU.
Skin microbial flora	Immediate skin-to-skin contact between the mother and newborn should occur in the delivery room right after birth, irrespective of how the delivery took place.
Hand hygiene	Rigorous hand cleanliness before and after caring for newborns.
Gloves	The rate of MSSA isolation drops when gloves are utilized as a method for infection control.
Prevent overcrowding	Prevent overcrowding by cohorting and isolating MSSA-positive neonates, implementing barrier precautions, training healthcare staff, and steering clear of congested wards

MSSA, methicillin-susceptible *Staphylococcus aureus*; NICU, neonatal intensive care unit.

A single isolate (TS1) was obtained from a lethal case of necrotizing pneumonia, while the remaining 19 PVL-MSSA isolates, encompassing both hospital-acquired and community-acquired strains collected from November 2008 to May 2009 (Table 2), were predominantly associated with skin and soft tissue infections. Seg and sei genes were found in 89.5% (17/19) of the isolates, which means that virulence/toxin genes are not very common in this population. The seb and tst genes were absent in this study group; only isolates of sequence type 722 (ST722) had up to four of the thirteen toxin genes analyzed (Table 2). In the same way, 89.5% (17/19) of isolates were resistant to trimethoprim, while 57.9% (11/19) of isolates were also resistant to gentamicin. The ST30 isolate TS12 was the most resistant to four antibiotics. Clindamycin, rifampin, linezolid, vancomycin, fusidic acid and teicoplanin, on the other hand, all worked against the isolates. Using the spa technique (StaphType software program; Ridom GmbH, Wurzburg, Germany), genotyping found two spa clonal clusters (CCs) (CC005 and CC345/657) and five singletons. The most prevalent types were T005

and T021 (47.4%), however there was only one test isolate for each of the other seven types. Three previously uncharacterized spa types (t6642, t6643, and t6769) were identified. Using eBURST software analysis, six MLST STs were found and put into five CCs of known MRSA lineages (CC1, CC22, CC30, CC88, and CC152). This showed even more strain variety. The most prevalent was ST22 (n = 9 [47.4%]), which has been directly associated with resistance to trimethoprim and gentamicin [37]. This study identified ST1518 (CC152) for the first time. This strain is a single-locus variant of ST152 that has a single mutation in the glp allele. It was discovered from a fatal instance of necrotizing pneumonia.

The PVL gene sequences from the study strains exhibited a total of seven SNPs, five of which were located in the lukS locus, in comparison to Φ SLT, the hypothesized lukSF-PV progenitor [39] (Table 2). The majority of isolates (n = 17; 89.5%) were classified as H variation, as delineated by O'Hara et al. [40], in the presence of both H1 and H2 groups. The R variation is only found in one isolate (TS1), which has the nonsynonymous nucleotide 527 A-to-G mutation. The PVL SNP profiles generated were often, but not always, unique to MLST. In ST30 isolates, there were two different PVL SNP patterns: H1 and H2. In 63.2% of isolates, the outlier H1 profile shown by TS12 was similar to that of ST22 and ST88 (12/19). Four different kinds of phages were found in the strains being studied: Φ PVL, Φ 108PVL, Φ Sa2USA, and Φ Sa2mw. All phage PCR findings for the ST772 isolates were negative, indicating an undetermined phage type. The only way to describe the phage identified in TS21 was by its form. In the majority of cases, a direct link between phage types and clonal lineage was seen. The ST30 isolates were more diverse since they had both Φ PVL and Φ 108PVL. On the other hand, all the ST22 isolates only possessed Φ PVL with its matching PVL SNP H2 profile. This group, together with the ST1 and ST88 isolates, didn't reveal any clear link between the kind of PVL phage and the PVL SNP profile. It was proven in TS25 that one isolate has a lot of distinct kinds of phages. TS18 and TS24 from the same patient were comparable, although TS17 from a relative was different at the spa locus. The TS6/9 cluster had the same characteristics as the epidemiologically linked isolates (Table 2).

There has been a lot of study on the molecular epidemiology of CA-MRSA [41,42], and people are becoming more interested in CA-MSSA, but not much is known about PVL-MSSA, notably the genetics of the lukSF-PV locus. In this study, we found that the MSSA isolates had major sequence types (ST22, ST88, ST30, and ST1) that were connected to PVL-MRSA clones [43,44,45]. While ST8, ST30, or ST80 make up most of the PVL-MRSA clones in the UK [46,47,48], the primary group we found in our study, ST22, also adds a lot to the burden of infection [46]. These strains are genetically comparable to the previously described ST22 PVL-MRSA strains from the United Kingdom in terms of susceptibility, toxin profile, and spa type [37]. They are not the typical hospital-acquired MRSA (HA-MRSA) ST22 EMRSA-15 clone. Our research found the same geographical and clonal bias in the distribution of the PVL haplotypes as had been shown before [45, 49]. This is because the R haplotype is only found in a few lineages, predominantly in the United States and more recently in Australia. The absence of R haplotypes in this limited study cohort may be attributed more to the methicillin susceptibility of the isolates than to their geographic origin, since previous studies have shown a significant presence of R haplotypes in several MRSA strains in the United Kingdom [37, 48]. The arginine (R)-to-histidine (H) mutation present in this haplotype is not considered to induce significant structural or functional alterations [50, 51]. However, it is important to highlight that the only R haplotype discovered in our investigation was associated with a fatal instance of necrotizing pneumonia in a healthy adult. One potential evolutionary process for the emergence of CA-MRSA is the acquisition of PVL genes prior to the SCCmec element. This study corroborated the hypothesis that PVL-MSSA and MRSA strains exhibit a considerable level of genetic similarity [52] by demonstrating that some clinical isolates of PVL-MSSA have spa and toxin gene profiles identical to those of previously documented PVL-MRSA clones. Our hypothesis is corroborated by the observation that several MSSA isolates in our study had PVL isoforms identical to those of previously characterized MRSA strains [37, 44,52]. It is possible for many evolutionary events to occur. While this necessitates confirmation, the identification of various PVL phage types within the ST30 lineage,

as observed in our analysis and documented by Boakes et al. in two additional studies [37, 53], may indicate the possibility of multiple phage acquisitions and, consequently, evolutionary processes.

4.2. Clinical Manifestations

Methicillin-susceptible *Staphylococcus aureus* (MSSA) infections significantly contribute to morbidity and death in neonatal intensive care units (NICUs). While research has mostly concentrated on MRSA strains, MSSA remains responsible for the bulk of clinical cases in newborns, exhibiting a range of presentations from superficial infections to severe, life-threatening syndromes.

Skin and soft tissue infections (SSTIs), which include pustules, abscesses, and cellulitis, are one of the most prevalent signs of this disease. Neonates are more susceptible to these factors owing to immature skin, intrusive procedures (such as intravenous catheters, sensors, and urine catheters), and proximity to healthcare staff and parents. Research indicates that these infections represent the predominant entrance point for bacteremia in newborns [31].

Bacteremia is the most severe and clinically significant symptom. MSSA accounts for a considerable percentage of sepsis cases in the NICU, with fatality rates ranging from 10% to 20% in some studies [30]. Bacteremia may manifest predominantly or secondarily with SSTI or pneumonia. The risk is greatly increased by the presence of central venous catheters and an extended hospital stay. Complications such as endocarditis and thrombophlebitis have been documented in MSSA bacteremia, even in newborns, but they are very uncommon.

MSSA pneumonia in newborns is infrequent, although it presents with a notably severe progression when it does. It may be primary or secondary, often occurring after aspiration or transmission via a ventilator. Necrotizing pneumonia, connected with the PVL gene, has been seldom reported, but with notable severity, even in MSSA strains [32]. This kind is marked by quick loss of the lung parenchyma, significant breathing problems, and a high death rate.

Other signs include osteomyelitis and septic arthritis, although these are more prevalent in older babies and kids. In newborns, when they manifest, they are often linked to hematogenous spread after sepsis. Early diagnosis is challenging owing to unique clinical presentation, and treatment delays result in severe consequences, including deformities or chronic inflammation.

Toxic shock syndrome (TSS) and enterotoxin food poisoning are significant concerns, notwithstanding their rarity in newborns. Even though they don't happen very often, they show that MSSA strains may make a lot of toxins and superantigens, which makes the overall clinical picture more complicated.

The intensity of the symptoms is contingent upon many conditions. Neonates with low birth weight (<1500g) and those born prematurely are at heightened risk for serious infections owing to their immature immune systems and the frequency of invasive treatments. Furthermore, colonization with MSSA serves as a significant prognostic indicator: a research by Toyama et al. [27] shown that the presence of MSSA in the nasopharynx correlates with an elevated risk of recurrent infection, particularly in newborns experiencing extended hospitalization.

Another defining trait is the comparable severity of MSSA and MRSA. Although MSSA is susceptible to traditional β -lactams, mortality and comorbidities do not substantially vary from those associated with MRSA [30]. This is likely attributable not to resistance, but to the diverse array of virulence factors inherent in MSSA strains.

In general, MSSA infections in newborns range from moderate skin infections to severe sepsis and necrotizing pneumonia. Their problems are just as significant as those of MRSA, and it's important to find them early and treat them.

4.3. Decolonization Strategies and Treatment Options for MSSAs

Methicillin-susceptible *Staphylococcus aureus* (MSSA) infections in newborns are not random; they are linked to specific risk factors pertaining to both the host and the hospital environment. Aiming at stopping, finding, and treating quickly and effectively, the following issues should be taken into consideration.

Premature newborns (<37 weeks of gestation), particularly those with very low birth weight (<1500g), have a significantly elevated risk of infection. Their immune systems aren't fully developed yet, so they can't quickly identify and destroy infections. Their thin skin and immature mucous membranes also don't work as good natural barriers [68]. In extensive multicenter investigations, low birth weight correlated with a two- to three-fold elevated risk of *S. aureus* sepsis, irrespective of methicillin susceptibility [30].

Central venous catheters, endotracheal tubes, urine catheters, and monitoring devices make it easier for the organism to get in. *S. aureus* may build biofilms on the surfaces of medical devices, which makes it harder for antimicrobials to work and helps it avoid the immune system [69, 70]. Milstone et al. [29] found that the presence of a central venous catheter was the best sign that a newborn had MSSA sepsis.

MSSA colonization of the nasopharynx and skin often occurs prior to infection. Colonization may occur by vertical transfer from the mother, horizontal transmission from healthcare professionals, or via surfaces in the NICU. A recent research in Japan found that MSSA strains taken from babies were genetically identical to those taken from staff. This shows that the nosocomial chain of transmission is a factor [27].

Being in the NICU for a long period constitutes a significant factor of risk. This is because, the longer is the hospital stay, the more likely there is a possibility of contracting MSSA by colonized people as well as places in which the bacterium has colonized and as a result there is need for the application of more invasive procedures. Studies show that the chance of contracting MSSA infection increases during the first week of life, especially in premature newborns [31].

Antibiotics, and more specifically broad-spectrum, may alter the typical microbial ecology of an infant, facilitating the proliferation and dissemination of MSSA. Exposure to cephalosporins and macrolides has been associated with an increased risk of MSSA infection [54]. On the other hand, relentless use of antibiotics may also make it hard to reach cure because they may contain strains that are resistant to later classes.

If the mother is infected by MSSA, whether it's a colonization or an active infection, the infant (especially in cases of preterm birth and cesarean delivery) bears a strong possibility to have it contracted [55].

Children with congenital heart disease, respiratory syndrome, or any other chronic health condition, are more prone to have an infection. Drug treatments or diseases that impair the immune system might increase the danger much more, although there has been acknowledge the way to control it.

Strategies that support infection prevention and control, such as hand hygiene, visitor restrictions, staff vaccination, infrastructure-related interventions and necessary isolation measures, contribute to a decrease in the rate of healthcare-associated infections and subsequently reduce antibiotic utilization [71, 72]. Additionally, a better knowledge of how important colonization is, has led to trial decontamination programs in NICUs, which have shown that MSSA infections are less often [55].

4.3.1. Precautions Against Colonization

Neonatal colonization with methicillin-susceptible *Staphylococcus aureus* (MSSA) is the first and most important link in the chain that might lead to infection. Because most infections in newborn intensive care units (NICUs) are caused by endogenous colonization or cross-transmission, preventative measures are aimed at stopping the formation of these infections and stopping the transmission of these diseases.

Careful hand hygiene is still the best and easiest way to stop colonization. Research indicates that the use of hand washing practices using alcohol-based solutions markedly reduces the spread of MSSA and MRSA in NICUs [56]. In addition, following aseptic protocols for any invasive operations (such as putting in a catheter or managing a ventilator) lowers the chance of introducing pathogens.

The hospital setting might serve as a reservoir for transmission. Surfaces, medical equipment and bed linens have tested positive for MSSA bacteria. Regular cleaning with antiseptic solutions and disinfecting equipment using technologies like ultraviolet light or hydrogen peroxide vapor have been found to be useful in lowering the environmental load [57].

A key technique is to actively manage colonization by taking samples from the nasopharynx, skin and other high-risk areas. Many NICUs do weekly or biweekly monitoring cultures. Finding carriers, whether they are newborns or healthcare workers, makes it possible to carry out targeted therapies [29].

Putting colonized or infected newborns in separate rooms or groups lowers the chance of cross-transmission. Studies suggest that this approach greatly lowers the number of MSSA colonization in at-risk individuals, even if it costs a lot to run [58].

There has been a lot of research on using mupirocin in the nose and mouthwash with chlorhexidine. In multicenter investigations, this approach decreased the occurrence of new MSSA and MRSA infections in NICUs by 30–50% [59]. However, these therapies should be used cautiously, since mupirocin resistance has been established [25].

4.3.2. Decolonization

Neonatal colonization by methicillin-susceptible *Staphylococcus aureus* (MSSA) is a major cause of infections in neonatal intensive care units (NICUs). Colonization normally starts before infections, thus decontamination treatments are aimed to interrupt this process and minimize the number of individuals who become ill or die.

Mupirocin, a topical antibiotic, is often used to decolonize the nasopharynx, the primary site of *S. aureus* infection. In randomized investigations, the administration of mupirocin to neonates with MSSA colonization significantly reduced the likelihood of infection development [59]. Simultaneously, its use among staff personnel harboring MSSA has aided in curtailing nosocomial transmission [25]. But the growing number of resistant strains makes it hard to use for a long time, thus focused usage and monitoring are needed.

Chlorhexidine is used to clean the skin from the outside in order to lower the number of microorganisms. In trials involving preterm newborns, consistent use of chlorhexidine solution baths correlated with a decrease in MSSA infections, exhibiting no significant side effects [29]. But it is important to be careful when using it on very preterm or very low birth weight babies (less than 1,000 g) since their skin is more permeable and it might be harmful.

The use of combination decolonization procedures has been shown to work better than monotherapy. A multicenter research shown that the combination of nasal mupirocin and chlorhexidine baths led to a 50% decrease in MSSA and MRSA infections in the NICU [59]. This technique is presently regarded as one of the most validated successful methods, however it requires vigilant oversight for potential resistance development.

Decolonization tactics apply not just to babies but also to those in close proximity to them. Research indicates that a considerable percentage of infected neonates originate from parents or healthcare providers who are carriers of MSSA [55]. Using mupirocin and chlorhexidine to decolonize these carriers locally, has been demonstrated to break the chain of transmission.

There is contention on the implementation of decolonization in a selective way (i.e., exclusively for neonates or personnel with positive cultures) or a universal application (to all individuals without exception). Targeted tactics lower the chances of developing resistance, whereas general techniques may quickly lower colonization but also raise the danger of choosing resistant strains [60]. Most ICUs want a balanced strategy that includes both surveillance management and targeted deployment.

Researchers are looking at novel ways to minimize colonization, such as probiotics, bacteriophages and antimicrobial peptides, in addition to traditional treatments. While evidence is still few, preliminary research indicates that probiotics may aid in the reestablishment of normal flora, hence decreasing the risk of *S. aureus* colonization [61].

It is very important to keep an eye on how decolonization is being put into action. To stay successful, it is important to do regular cultures, keep an eye on resistance indicators and check staff compliance.

4.3.3. Antimicrobial Therapy

Choosing the proper antibiotic for newborns with methicillin-susceptible *Staphylococcus aureus* (MSSA) infections is highly crucial since these individuals are more likely to have serious issues. MSSA is different from MRSA since it is susceptible to methicillin. However, clinical experience shows that the severity of infections may be similar, thus a strong and quick treatment plan is needed.

Oxacillin and nafcillin are two isoxazolympenicillins that are the best antibiotics for treating MSSA infections. They have shown efficacy and rapid bactericidal activity against MSSA strains [62]. They should be used for severe infections such pneumonia, sepsis and infections of the bones and joints. For babies, the dose should be altered based on their weight, how far along they are in their pregnancy and their kidney function.

Cefazolin is a different way to treat MSSA infections and it can be held as an efficient treatment in addition to safe. It is often used for skin and soft tissue infections, as well as in mild instances of sepsis. Some regimens recommend cefazolin over oxacillin because it is less harmful to the liver and easier to take [63].

Aminoglycosides, including gentamicin, are often used in conjunction with β -lactams during first empirical treatment, particularly for severe infections. This combination has a synergistic effect, which speeds up the removal of bacteremia [26]. However, since they might be harmful to the kidneys and ears, they should only be used for a limited time (typically less than five days) and then followed by monotherapy.

Vancomycin is often used for MRSA infections; however, it is not a primary treatment for MSSA. Research indicates that MSSA infections managed with β -lactams have a more favorable outcome compared to those treated with vancomycin [64]. Vancomycin is only used when someone is allergic to penicillin or has more than one illnesses. Linezolid is not usually used for MSSA, however it could be an option for those strains who are resistant to other antibiotics or for people who have severe sensitivities.

Clindamycin is extensively used to treat skin and soft tissue infections because it penetrates tissues well and stops the formation of toxins. Some countries use fusidic acid with other antibiotics, although there isn't a lot of evidence on how well it works in infants [54].

The duration of the therapy depends on the kind and severity of the infection. For simple bacteremias, a treatment duration of at least 10 to 14 days is recommended; however, for more difficult diseases such as endocarditis or osteomyelitis, the duration may extend to 4 to 6 weeks [65]. The decision should be based on the clinical presentation and the individual's response.

In addition to focused antibiotic treatment, supportive measures are also highly important. These include taking out dirty catheters, ensuring sure the individual eats enough, and in certain cases, providing immunoglobulins to stimulate the immune system [66].

Even though there are effective treatments for MSSA infections, it's still challenging to treat them in neonates since not enough study has been done. Because neonates are so delicate, it is crucial to pick the proper medicine and dosage carefully. The increase of resistance to aminoglycosides and clindamycin limits treatment options. Future endeavors include the development of novel antistaphylococcal agents and the incorporation of immunotherapeutic strategies.

Table 3. Antibiotics according to gene resistance.

Antibiotic class	Main resistance genes	Mechanism	Clinical relevance	References
β -lactams (penicillin, ampicillin)	blaZ	Production of β -lactamase hydrolyzing natural penicillins	>80–90% of MSSA isolates resistant to penicillin; limits use of older β -lactams	Becker et al., 2014
Macrolides, lincosamides, streptogramin B (MLSB)	erm(A), erm(C)	23S rRNA methylation $\rightarrow$ ribosomal target modification	Inducible or constitutive resistance; therapeutic failures with clindamycin/erythromycin	Leclercq, 2002
Tetracyclines	tet(K), tet(M)	Efflux pump (tetK), ribosomal protection (tetM)	Reduced efficacy of tetracyclines in skin/soft tissue infections	Roberts, 2005
Fusidicacid	fusB, fusC, fusA mutations	Protection or modification of EF-G elongation factor	High resistance rates in countries with frequent fusidic acid use	O'Neill&Chopra, 2006
Mupirocin	mupA, mupB, ileS mutations	Alteration of isoleucyl-tRNA synthetase	Resistance compromises nasal decolonization strategies in NICUs	Patel et al., 2009
Aminoglycosides (gentamicin, tobramycin, kanamycin)	aac, ant, aph	Enzymatic modification (acetylation, phosphorylation, adenylation)	Reduces synergistic use with β -lactams in severe infections	Chandrakanth et al., 2008

MSSA, methicillin-susceptible *Staphylococcus aureus*; NICU, neonatal intensive care unit.

5. Discussion

This investigation shows that methicillin-susceptible *Staphylococcus aureus* (MSSA) is still a major pathogen in neonatal intensive care units (NICUs), and its clinical and epidemiological importance is frequently not fully appreciated. Worldwide literature has mostly focused on methicillin-resistant strains (MRSA); however, current data suggest that MSSA infections are more common and exhibit clinically equivalent severity [27,30].

An analysis of molecular characteristics confirmed that MSSA strains had a diverse range of virulence factors, including hemolysins, toxins, and mechanisms for biofilm development. This corroborates Otto's [67] results, which demonstrated that the pathogenicity of *S. aureus* transcends resistant strains and is associated with the production of exotoxins and superantigens. The finding that PVL-positive MSSA strains may cause necrotizing pneumonia is significant, supported by the study of Otokunefor et al. [32], which associated MSSA clones with the PVL gene to severe pneumonia cases and extensive skin and soft tissue infections. Consequently, this aspect emphasizes that sensitivity to methicillin does not reduce pathogenicity. The study showed that MSSA bacteria

are still susceptible to β -lactams, but they are quite resistant to other groups, such as aminoglycosides and clindamycin. This corresponds with the results of Chandrakanth et al. [26], who discovered several resistance mechanisms in multidrug-resistant clinical MSSA isolates. At the same time, the study by Turner et al. [54] highlighted that the development of resistance beyond the SCCmec element has been a common phenomenon, stressing the need for prudent antibiotic use even in MSSA infections. Consequently, while the literature often categorizes MSSA as a “susceptible” condition, the reality suggests that resistance to certain medications may complicate clinical management.

The findings of the present review indicate that MSSA infections are three to four times more common than MRSA in ICUs, supporting the results of Geng et al. [22] in a Chinese cohort and Milstone et al. [29] in a multicenter study in the USA.

Conversely, research from Asian locations, shown by the study conducted by Hong et al. [13], indicates a heightened prevalence of MRSA strains. This difference likely indicates local epidemiological pressures, antibiotic use policies and infection control initiatives. Nonetheless, the unifying aspect of this research is that MSSA is not a “secondary” pathogen, but a primary source of infections in the NICU.

The current findings corroborates the significance of colonization, since it almost invariably precedes infection. This study corroborates the seminal research conducted by Wertheim et al. [28], which established nasal colonization as a significant predictor of *S. aureus* infection. Moreover, the recent work by Toyama et al. [27] demonstrated genetic relatedness between strains from newborns and healthcare personnel, hence affirming the significance of the nosocomial chain of transmission.

The identified risk factors—prematurity, low birth weight, extended hospitalization, and the use of invasive devices—align with findings from extensive epidemiological research [31,68]. Specifically, the presence of central venous catheters is generally acknowledged as the most significant predisposing factor for MSSA sepsis [29]. Moreover, the correlation between maternal colonization and newborn colonization [55] substantiates the need for preventative interventions to include not only the hospitalized infant but also the parents.

MSSA infections have a clinical range that includes SSTIs, severe bacteremias and pneumonia. Our research demonstrated that bacteremia is the most clinically significant manifestation, with a mortality rate equivalent to that of MRSA, a result consistent with the multicenter study conducted by Benjamin et al. [30]. Simultaneously, the infrequent but profoundly severe necrotizing MSSA pneumonia delineated by Otokunefor et al. [32] underscores the clinical significance of MSSA clones possessing PVL genes. In general, the information in this study shows that being susceptible to methicillin does not mean that the disease will be less severe.

The review demonstrated that decolonization with mupirocin and chlorhexidine significantly reduces infections. Studies like Huang et al. [59] have shown that infections in the ICU might happen up to 50% less often. Nonetheless, the probabilistic emergence of mupirocin resistance, as delineated by Patel et al. [25], is a significant constraint. Consequently, focused techniques are seen superior than general approaches, a position also endorsed by Septimus & Schweizer [60].

The preferred therapy for MSSA infections continues to be β -lactams, supported by robust clinical data [62]. Our findings corroborate those of Chang et al. [64], which demonstrated that the treatment of MSSA bacteremia with β -lactams results in superior clinical outcomes relative to vancomycin. Simultaneously, the use of cefazolin seems to be a viable option with a favorable safety profile (Lee et al., 2018). The need for combination with aminoglycosides in the first phase aligns with the findings of Chandrakanth et al. [26]; however, the possible toxicity restricts the length of therapy.

The findings, when compared to global literature, demonstrate that MSSA is an underestimated but clinically relevant disease. The results confirm the continuing importance of MSSA epidemiology, the seriousness of infections and the necessity for decontamination and preventive measures. The differences across countries, like Europe and Asia, highlight how crucial it is to keep an eye on how diseases grow in each area and adjust how you do things as necessary.

6. Conclusions

This narrative review has shown that methicillin-susceptible *Staphylococcus aureus* (MSSA) infections in neonates remain a considerable public health concern, notwithstanding the increased research focus on resistant strains (MRSA). Our findings demonstrate that MSSA is the primary pathogen in neonatal intensive care units (NICUs), with clinical manifestations ranging from basic skin infections to severe sepsis and necrotizing pneumonia [30,32].

Molecular findings validate previous studies, indicating that MSSA strains have similar pathogenic potential to MRSA, due to the presence of hemolysins, toxins, and the ability to form biofilms (Otto, 2014). For example, PVL-positive MSSA strains have been related to highly severe infections, which suggests that the bacteria are still harmful even if they don't have the SCCmec characteristic. This discovery emphasizes the need of addressing MSSA infections with the same rigor as MRSA.

Epidemiological statistics reveal that MSSA infections are more common than MRSA infections in most places, with ratios of 3:1 to 4:1. This is based on studies done in China, Europe, and the United States [22, 27]. Nonetheless, regional inequalities, shown by the frequency of MRSA in several Asian areas [13], highlight the need for continuous local surveillance. The outcome indicates that MSSA is not a "milder" illness; it is often the predominant bacteria in ICUs.

The risk variables we have identified—prematurity, low birth weight, extended hospital stay and the use of invasive catheters—align with the results of extensive multicenter investigations [31, 68]. Additionally, the correlation between maternal colonization and newborn colonization [55] indicates that preventive measures should include not just the NICU but also the familial context. The fact that colonization nearly often comes before infection [28] suggests that decolonization measures are very important.

Decolonization with mupirocin and chlorhexidine has shown effectiveness in reducing infections [59]; however, the potential for mupirocin resistance emergence [25] limits its extensive use. The evidence suggests more targeted therapies for high-risk babies, together with strict hand cleanliness and environmental control [56, 57].

At the treatment level, β -lactams continue to be the most effective option for MSSA infections, with better outcomes than vancomycin [62,64]. Cefazolin seems to be an excellent choice for newborns since it is very safe (Lee et al., 2018). Combining with aminoglycosides may be useful in severe infections, but their toxicity necessitates prudence and a restriction on the length of dosing [26].

The findings indicate that MSSA infections in newborns are not less severe than those caused by MRSA. Pathogenicity, prevalence and mortality need the formulation of comprehensive preventive, decontamination and treatment measures. The findings of this review align with worldwide literature, indicating that methicillin susceptibility does not signify diminished clinical relevance.

Nevertheless, significant deficiencies are noted: the bulk of research focuses on MRSA, whereas MSSA is little represented, especially in NICUs. Furthermore, the variability in decontamination techniques and the lack of long-term data hinder the ability to reach conclusive determinations. Subsequent study need to concentrate on formulating novel preventive techniques, like the utilization of probiotics or alternative disinfectants, alongside the establishment of newborn registries to precisely record MSSA prevalence.

In conclusion, MSSA, despite its susceptibility to methicillin, continues to be a critical pathogen in the NICU, associated with considerable morbidity and death. A multi-level intervention approach should be prioritized, including prevention, decolonization, early diagnosis, and tailored treatment, to alleviate the challenges faced by this vulnerable community.

Author Contributions: Conceptualization, A.N. and V.G.; methodology, A.N. and V.G.; validation, A.N. and V.G.; formal analysis, A.N.; investigation, A.N.; writing—original draft preparation, A.N.; writing—review and editing, A.N., M.B., N.C., N.D., C.-M.T., F.B. and V.G.; supervision, V.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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