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Fulminant Staphylococcal Infections

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ABSTRACT Fulminant staphylococcal infection indicates an explosive, intense, and severe infection occurring in a patient whose previous condition and antecedent would never have caused any anticipation of life-threatening development. This includes necrotizing pneumonia, necrotizing fasciitis, and to some extent toxic shock syndrome and infective endocarditis. In the three former diseases, toxin production plays a major role whereas in the latter (fulminant presentation of infective endocarditis), association with any particular toxinic profile has never been demonstrated. This article reviews the clinical, pathophysiological, and therapeutic aspects of these diseases.

INTRODUCTION

Fulminant infections are not clearly defined in the field of staphylococcal infections. According to Wikipedia, "fulminant" is a descriptor, especially used in the field of medicine, for any event or process that occurs suddenly and escalates quickly and is intense and severe to the point of lethality, i.e., it has an explosive character. The word comes from Latin *fulminare*, to strike with lightning. For staphylococcal infections in which, despite the fact that *Staphylococcus aureus* is considered a commensal, progression may be devastating in many circumstances, it appears pertinent to add to this definition the notion of an unexpected event leading to a "thunderstorm in a quiet blue sky." Hence, fulminant staphylococcal infection indicates an explosive, intense, and very severe infection occurring in a patient whose previous condition and antecedent would never have suggested any anticipation of life-threatening development. Considering this definition, fulminant is an adjective that could be associated with several staphylococcal infections, including necrotizing pneumonia, necrotizing fasciitis, and to some extent toxic shock syndrome and infective endocarditis (IE). In the three former diseases, toxin production plays a major role, whereas in the latter (fulminant presentation of IE), association with any particular toxinic profile has never been demonstrated.

STAPHYLOCOCCAL NECROTIZING PNEUMONIA

The role of *S. aureus* in pneumonia has been known for decades, but staphylococcal pneumonias are rare, representing only 2% of community-acquired pneumo-

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nia in adults (1). Until the end of the 20th century, *S. aureus* was thought to be responsible for community-acquired pneumonia in two main circumstances: first, in respiratory diseases of adults, *S. aureus* pneumonia is observed mainly in the elderly and/or associated with underlying conditions such as immunodepression, cancer, diabetes, or chronic respiratory disease. *S. aureus* is also a major cause of exacerbation in cystic fibrosis. Moreover, *S. aureus* is responsible for 20 to 30% of health care-associated respiratory infections, particularly ventilator-associated pneumonias (2). In such situations, no specific staphylococcal virulence factors are clearly associated with staphylococcal pneumonia, and the main issue for the clinician is to manage methicillin-resistance and multidrug resistance, which are common in hospital-acquired cases. These staphylococcal pneumonias are often severe, but it is always difficult to determine the role of the intrinsic virulence of *S. aureus* or the patient's underlying condition in the potentially unfavorable evolution. The second presentation of severe staphylococcal pneumonia used to be observed only in very young children, aged less than 1 year (3). This disease was commonly described as a bilateral multifocal round-shaped pneumonia with bullous formations in lung parenchyma, leading sometimes to the appellation "bullous pneumonia," considered in children as pathognomonic of *S. aureus* (4). Pleural effusion was common, as was combined pleural empyema and pneumothorax secondary to rupture of bullous lesions in the pleural cavity (5). This severe presentation was associated with a high case-fatality rate, from 10 to 23% (3, 6). Although most cases in the years 1960 to 1970 were associated with the phage type 80-81, now known to encompass strains encoding the Panton-Valentine leukocidin (PVL) (7), no specific staphylococcal virulence factor was identified in staphylococcal pleuro-pneumonia of young children (7). For partially unknown reasons, staphylococcal pneumonia almost disappeared in children in developed countries at the end of the 20th century, whereas it was still commonly described in low-income areas. Nevertheless, despite the undeniable severity of staphylococcal pneumonia, fulminant presentations as defined above were considered very rare, and evolution toward a fatal outcome was usually attributed to underlying conditions rather than to staphylococcal virulence. However, case reports and even small series of fulminant staphylococcal pneumonia were sporadically reported in older children and young adults, but the basis of the severity in these cases has remained unknown.

The first step in understanding how virulence factors impact the severity of staphylococcal pneumonia was reached in 1999, when Lina et al., studying a collection of 172 strains referred to the French National Reference Center for Staphylococci (*Centre National de Référence des Staphylocoques*), showed that 85% of the strains isolated from severe community-acquired pneumonia harbored *luk*S-PV and *luk*F-PV genes, together encoding a rare (less than 5% of strains in Europe) (8) staphylococcal exotoxin: the PVL (9). The clinical presentation of these pneumonias was very unusual in view of their severity (lethality, >75%) but also in view of their epidemiology and symptoms: the cases were observed in young immunocompetent patients but not in very young ones, and most of the patients showed signs of pulmonary necrosis with massive airway bleeding. The complete clinical and biological characterization of this particular form of staphylococcal pneumonia in humans and its link to the presence of *pvl* genes was achieved by a prospective comparison between PVL-positive and PVL-negative strains causing community-acquired pneumonia (10). As prospective surveillance continued in France, features associated with severity and mortality were identified (11). Hence, a rare but severe presentation of staphylococcal pneumonia was described and named "staphylococcal necrotizing pneumonia" (SNP). The main clinical characteristics of this disease can be summarized as:

- Occurrence in most cases in young immunocompetent patients, without an antecedent or underlying condition.
- Preceding flu-like illness, with documentation of influenza virus infection in some cases.
- Rapidly progressive bilateral pneumonia, without bullae, evolving toward severe hypoxemia and pulmonary edema and leading to acute respiratory distress syndrome.
- High frequency of airway hemorrhages, massive in some cases.
- Initial leukopenia.
- High case-fatality rate despite young age and absence of underlying preconditions. For the fatal cases, death occurs promptly after the onset of the disease (median survival time, 4 days).
- Unusual pathologic findings on lung necropsy: necrotic destruction of the entire respiratory epithelium, from larynx to alveoli in some cases, without polymorphonuclear infiltrate. Diffuse alveolar damage with hemorrhagic infiltration.

In the comparative study of community-acquired staphylococcal pneumonia based on toxin profiling (12), all the cases matching the above description of necrotizing pneumonia were caused by PVL-positive strains, whereas bilateral pneumonia caused by PVL-negative strains was commonly seen in the elderly and was associated with underlying preconditions. In PVL-negative cases, fulminant evolution was not observed, and leukopenia, airway bleeding, and signs of lung necrosis were absent. These differences suggest that PVL and likely other pore-forming toxins play a central role in the pathophysiology of necrotizing pneumonia.

Since its first description in 2002, (SNP) has been reported worldwide (13–17), and in all cases, the causal strains, despite their genetic diversity and lack of clonality, harbored the *pvl* genes on various prophages (reviewed in reference 18), which is presumably responsible for their dissemination among unrelated strains. Moreover, the finding that previously published cases of fulminant staphylococcal pneumonia had clinical presentations very similar to the "typical" features of SNP (19, 20) may indicate that this disease, although not formally recognized, had been encountered for many years and should not be considered an emerging entity. A particular situation concerning SNP is observed in the United States, where the description of SNP coincided with the emergence of the USA300 community-associated methicillin-resistant *S. aureus* (CA-MRSA) lineage; indeed, almost all the reported cases in the United States were due to USA300 (17, 21, 22). This particular lineage restriction in the United States led to confusion in the understanding of the determinant of severity associated with SNP. First, methicillin resistance was thought to be a major determinant of severity, presumably by inducing a delay in initiation of appropriate antibiotics. However, it has now been demonstrated that methicillin resistance *per se* is not associated with higher mortality in SNP (23) and, despite probable overreporting of cases due to MRSA, more than 70% of the cases of SNP in Europe are due to methicillin-susceptible *S. aureus* strains belonging to distinct lineages. Second, the restriction to USA300 leads to an overestimation of the role of this clone's specific virulence factors. An enhanced production of alpha-hemolysin (24, 25) or phenol-soluble modulin (25, 26) and the presence of Arginine Catabolic Mobile Element (ACME), which is strongly associated with USA300 (27), were therefore suspected to be major determinants of severity in SNP, minimizing the potential role of other virulence factors such as PVL (28). However, the low prevalence of *pvl* genes in strains circulating in Europe (8) and the absence of clonality of infection strains presented a unique opportunity to determine whether or not PVL was associated with severity and poor outcome of staphylococcal pneumonia (29). Apart from the epidemiological association of PVL with the severity of community-acquired pneumonia (10, 13), other features suggest that PVL contributes to the severity of SNP: interestingly, the most typical clinical and biological features associated with SNP, i.e., leucopenia and airway hemorrhages, although they are not fully specific, are strongly associated both with its severity and with the known biological effect of PVL. Hence, leucopenia is probably the result of the lytic effect of leukotoxins on polymorphonuclear (PMN) cells. Leucopenia is associated with mortality in various studies (11, 16, 17), and we have shown that the association of leukopenia with death is "dose-dependent": when the total leucocyte count was above 3 giga elements/liter at hospital admission, survival was observed in >75% of cases, whereas less than 20% of the patients survived when their leucocyte counts were <3 giga elements/liter (11). Airway hemorrhage is associated with poor prognosis too and is a direct consequence of the massive necrosis of the respiratory epithelium, likely due to the direct and indirect leukotoxic properties of PVL and not observed in other staphylococcal pneumonias.

Animal models are required to fully understand the complex interactions between *S. aureus*' virulence factors, host susceptibility, and severity. The model should reproduce the phenotype observed in humans with necrotic hemorrhagic lesions and pulmonary edema. The first model of necrotizing pneumonia was developed in BALB/c mice with nasal instillation of high inoculum (30). Necrotic lesions were observed, but survival of the infected mice was impaired only when overexpressing *pvl* on multicopy plasmids. Other studies in mice failed to demonstrate any role for PVL in severity and even to induce necrotic lesions (24). It is now widely accepted that PVL is poorly active toward murine leucocytes while being highly cytotoxic toward human and rabbit leucocytes (31). The identification of human C5aR and CD45 as the receptors for LukS-PV and LukF-PV, respectively, at the surface of phagocytes offered a molecular explanation for the lack of relevance of mouse models for the study of PVL-associated pathogenesis (31–33). Indeed, due to polymorphisms between mice and humans, neither LukS-PV nor LukF-PV bind to murine C5aR1 and murine CD45, resulting in PVL being inactive in mice. In contrast to murine C5aR1, rabbit C5aR1 is compatible with LukS-PV, and rabbit PMN cells are highly susceptible to PVL, making this species

a relevant animal model for studying the role of PVL in SNP.

Diep et al. developed a convincing rabbit pneumonia model using inocula 10-fold lower than those previously used in mice (34). In this model, nasal instillation of a PVL-positive CA-MRSA USA300 strain is associated with activation of PMN cells and alveolar macrophages, leading to the direct destruction of PMN cells by PVL and intense production of inflammatory mediators, particularly interleukin 8 (IL-8). These mediators attract more and more PMN cells, whose PVL-induced lysis and degranulation liberates proteases and oxidative products. These toxic components provoke vasodilatation, pulmonary edema, and cellular lesions, leading to hemorrhagic necrosis of the pulmonary epithelium (34), mimicking the pathology observed in human necropsies. The central role of PMN cells in the pathogenesis of lesions observed in SNP is emphasized in this model by the absence of Il-8 production, pulmonary edema, and necrotic lesions in neutropenic rabbits exposed to a high concentration of PVL (34). Alveolar macrophages and lung epithelial cells may play a key role in the initiation of inflammation since PVL not only lyses PMN cells directly but also triggers IL-1β release in human alveolar macrophages, which in turn stimulates the massive secretion of the neutrophil-attracting chemokines, IL-8 and monocyte chemotactic protein-1, by lung epithelial cells (35). Interestingly, this inflammatory pathway is amplified by the release of pathogen- and damage-associated molecular patterns from dying neutrophils, possibly explaining the fulminant nature of SNP (36). Of note, the PSMalpha3, beta-, gamma-, and delta-hemolysins and LukDE synergize with PVL to amplify IL-1β release, indicating that these factors cooperate with PVL to trigger inflammation (35). Another issue in deciphering the complex pathophysiology of necrotizing pneumonia is to determine the putative role of influenza virus in the infection. Epidemiological links appear in many studies (11, 17, 22, 37, 38), but interactions between both pathogens remain hypothetical. However, two distinct mechanisms are probably involved: first, influenza infection may favor *S. aureus* attachment, causing epithelial lesions which expose basal layers of mucosae with matrix components to which *S. aureus* adheres (39, 40). Second, animal experiments indicate that influenza may play a role in PMN cell recruitment in the lungs, triggering inflammatory signals (41, 42). Considering the central role of PMN in necrosis induction and the near absence of PMN cells in normal lungs, it is tempting to hypothesize that this PMN recruitment is a key point for necrosis induction mediated by PVL (41).

Altogether, fulminant *S. aureus* pneumonia occurring in patients without known predisposing factors is strongly associated with PVL-producing strains, and most *in vitro* and animal model data reveal that this observation is beyond simple association. However, two major issues remain to be addressed: first, even if the prevalence of the *pvl* genes is low in the general population (8), the carriage rate of *S. aureus* in humans is sufficiently important so that millions of people are exposed to PVL-producing strains; yet the incidence of fulminant *S. aureus* pneumonia remains extremely low, i.e., 30 to 50 cases per year in a 60-million-inhabitant country like France in which there should be roughly 1 million carriers of PVL-positive *S. aureus* (CNR annual report, http://cnr-staphylocoques.univ-lyon1.fr/). It is thus tempting to speculate that factors other than PVL and/or a genetic predisposition to PVL are required for the development of these fulminant presentations of pneumonia. Susceptibility to *S. aureus* infections can be linked to specific human mutations. Rare mutations affecting the Toll-like receptor/IL-1 receptor pathway, the IL-17 pathway, and the NADPH oxidase pathway are strongly associated with recurring or severe *S. aureus* infections (for review see reference 43). Two genome-wide association studies have been performed to identify genes influencing *S. aureus* diseases, highlighting several candidates (44, 45). However, so far, no specific polymorphism has been associated with the development of fulminant *S. aureus* pneumonia. The contributing role of other virulence factors and toxins is another issue to be explored. Indeed, not all fulminant *S. aureus* necrotizing pneumonias are caused by PVL-producing strains, suggesting the involvement of other potentially necrotizing toxins such as alpha-toxin, gamma-hemolysins, or LukGH that are present in most *S. aureus* strains (8, 46). Indeed, alpha toxin is most likely the major pore-forming toxin in *S. aureus* and is known to contribute to the severity of *S. aureus* pneumonia and other infections (47), while the gamma-toxin HlgCB, which targets the C5aR on myeloid cells, as does PVL (48), could be a major contributor. Under what circumstances these toxins could determine fulminant pneumonia remains to be explored, but large variations in the expression of these toxins *in vivo* (49) is an important parameter to be considered.

The existence of staphylococcal lung infection, due to a proven "toxinic" strain, which secretes a large amount of PVL or some other pore-forming toxin, is not necessarily associated with a fulminant course even when clinical evidence of necrosis is observed. Hence, especially in young children, PVL-positive strains are pre-

dominant in staphylococcal pneumonia, in both the United States and in Europe and are associated with necrotic abscesses and pleural effusion (50, 51), but in these studies, symptoms of fulminant necrotizing pneumonia were rarely observed and mortality was <5%. In fact, the description of most of the cases matches the classic presentation of staphylococcal pleuro-pneumonia of young children, often caused by the notorious 80-81 epidemic strain, which probably produced PVL, and an unresolved challenge is to understand why in some cases, PVL-positive *S. aureus* lung infection provokes fulminant lung necrosis, whereas in other cases, necrosis is limited to abscess formation, and the outcome is far less devastating. Differential levels of virulence factor expression including that of the core-genome-encoded pore-forming toxins or patient heterogeneity regarding toxin susceptibility may contribute to these differences, but these explanations remain largely hypothetical. Another hypothesis involves the pathophysiology of lung infections. Lung invasion can be secondary to the hematogenous spreading of septic emboli from a distant infection focus; however, *S. aureus* can also directly reach the lung via the inhalation route. In the first case, necrotic effects would involve predominantly conjunctive lung tissue, and the necrotic lesion would be a localized abscess; in cases of inhalation, necrotic lesions should be more diffuse and should involve the respiratory epithelium directly, leading to major and prompt alteration of respiratory function. Currently, this distinction is purely theoretical, although some evidence from the rabbit model favors this pathophysiological model (52).

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is another rare disease that matches (in some instances) our definition of fulminant staphylococcal infection. TSS was described in 1978 in seven children aged 8 to 17 years (53). Despite the severity of the disease, *S. aureus* was isolated only from mucosal sites, while blood, cerebrospinal fluid, urine, and other potential infectious sites remained sterile, leading a toxin-mediated phenomenon to be suspected. Despite the fact that similar cases had been previously described, J.K. Todd was the first to describe these cases as a specific clinical entity. A few years after the initial description, the United States faced an "outbreak" of TSS in young women who presented typical and often severe forms of TSS during their menses (54–56). This presentation was identified as menstrual TSS (mTSS) and was initially attributed to the use of hyper-absorbent tampons, but it became rapidly apparent that all kinds of tampons could be involved (57). More recently, mTSS was associated with other devices, such as menstrual cups (58). After the withdrawal from the market of the incriminated tampons and information campaigns about this syndrome in the United States, the incidence of mTSS dramatically fell (although mTSS did not disappear), and TSS not associated with menstruation was therefore "rediscovered" (59). The nonmenstrual forms of TSS (nmTSS) are quite similar in their clinical presentation but lead to higher mortality rates (60). nmTSS are usually associated with a staphylococcal deep-seated focus of infection (61), whereas menstrual cases are associated with vaginal carriage (60).

The clinical features of TSS have been remarkably consistent since the initial description and are associated with several nonspecific features, the combination of which leads to the diagnosis. TSS is thus diagnosed in the face of a rapidly deteriorating condition associate with an infectious syndrome, with muco-cutaneous involvement and hemodynamic failure (61). At the initial stage, the patient presents with a flu-like syndrome associated with fever, headache, chills and muscle pain, sore throat, and often diarrhea (62). Even if they are observed in a young woman during menses, none of these symptoms nor their association are specific, and although not clearly documented, some cases spontaneously resolve by the end of the menstruation and the removal of the tampon (Y. Gillet, unpublished data). A few hours after, in a case progressing toward true TSS, the patient presents with a generalized cutaneous rash, which is sometimes described as "sunburn-like," but even if it may be itchy, the rash is usually not painful (63). The clinical aspect of the cutaneous eruption is not specific but usually involves the extremities with local edema and redness. Such involvement of palms and soles, unusual in other diseases (i.e., in viral rashes), may point toward the diagnosis of TSS. Finally, if the patient survives, rash is followed 10 to 15 days after the onset of the disease by a spectacular desquamation typically involving the whole palms and soles. Concomitant with the rash, mucosal involvement is constant but may be delayed a few days. Lips are dry and bright red, the tongue is red with a "strawberry" aspect, and the eyelids become inflammatory with a bilateral conjunctivitis without purulent exudate (61, 64). Genital mucosae are inflammatory too, usually without purulent discharge. Simultaneously or rapidly after the onset of the rash, the patient's general status worsens and hemodynamic failure appears. As with other infectious shock syndromes, the mechanisms of hypotension are multiple: dehydra-

tion due to diarrhea, hypovolemia caused by capillary leakage, and vasodilatation and lowering of cardiac output secondary to direct cardiac dysfunction (63). In the most severe cases, the physiological compensation for circulatory insufficiency may provoke intense vasoconstriction of the skin, leading the erythematous eruption to be unapparent. Diagnosis is particularly difficult in such situations and is often delayed until hemodynamic improvement reveals the rash (Y. Gillet, unpublished data). Moreover, although hypotension is by definition required for the diagnosis of TSS, there are many different clinical presentations in terms of severity, from simple malaise with orthostatic hypotension to refractory shock unresponsive to remediation, even if prompt, and leading to multiorgan failure (61). These potential marked differences in terms of intensity of the hemodynamic failure are unfortunately not always taken into account in studies and may result in misinterpretation, especially in the field of treatment strategies. Obviously, less severe cases are more likely to be self-limited, whereas severely ill patients should benefit more from specific intervention. Therefore, one should keep in mind that the acronym TSS embraces a large diversity of diseases, from self-limited to life-threatening, with only the latter falling into the above definition of fulminant disease. Nevertheless, as mentioned before, none of the symptoms of TSS could be considered specific, and the diagnosis is based on the criteria (65) listed in Table 1.

Interestingly, the presence of *S. aureus* is not required according to the CDC's criteria, since very severe TSS can be observed during *Streptococcus pyogenes* infections with only subtle clinical differences from nmTSS (66).

Despite the above well-defined criteria and the fact that TSS is a reportable disease in many states in the United States (67), the incidence of TSS is not precisely known. Some cases are unrecognized either because they are not severe enough and are self-limited or because of extreme severity leading to prompt death before recognition of the syndrome. However, the incidence in the United States is estimated to be from 1 to 3 per 100,000 inhabitants (56, 59). The incidence is 2-fold higher in women between 13 and 24 years old, and menstrual forms represent 54% of the identified cases (59).

In both mTSS and nmTSS, staphylococcal exotoxins with superantigenic properties are involved. mTSS and, to a lesser extent, nmTSS, are "true toxin-mediated diseases" (toxinoses), meaning that all the observed symptoms can be explained by the action of the exotoxins, without involvement of other staphylococcal virulence factors. *S. aureus* can produce 24 exotoxins with superantigenic properties (68), but most cases of TSS are due to the following four of them, in decreasing order of incidence: toxic shock syndrome toxin-1 (TSST-1), *Staphylococcus* enterotoxin A (SEA), SEC, and SEB (59). The structure of TSST-1 is remarkable by the presence of a peptidic loop dedicated to intraepithelial transportation by a hypothetical carrier and conferring to TSST-1 its unique ability to cross the mucosal barrier (69). Therefore, TSST-1 is associated with >90% of mTSS (59, 60), whereas it is present in only 50% of nmTSS (59). Mucosal lesions induced by staphylococcal cytolysins may also play a role in the transmucosal crossing of TSST-1 (69). Staphylococcal superantigens are active at very low concentrations and induce a polyclonal activation of T lymphocytes by mediating a

TABLE 1 Case definition of staphylococcal TSS

Clinical criteria
Body temperature >38.9°C (102.02°F)
Systolic blood pressure <90 mmHg
Diffuse macular erythroderma
Desquamation (especially of the palms and soles) 1–2 weeks after onset
Involvement of three or more organ systems:
Gastrointestinal (vomiting, diarrhea)
Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal for laboratory
Mucous membrane hyperemia (vaginal, oral, conjunctival)
Kidney failure (serum creatinine >2 times normal)
Liver inflammation (bilirubin, Aspartate Aminotransferase (AST), or Alanine Aminotransferase (ALT) > 2 times normal)
Low platelet count (platelet count <100,000/mm^3)
Central nervous system involvement (confusion without any focal neurological findings)
Laboratory criteria
Negative results of the following tests, if performed:
Blood, throat, and cerebrospinal fluid cultures for bacteria (besides *S. aureus*)
Serology for *Rickettsia* infection, leptospirosis, and measles
Case classification
Confirmed: All six of the criteria above are met (unless the patient dies before desquamation can occur)
Probable: Five of the six criteria above are met

direct interaction between the major histocompatibility complex class II receptor on antigen presenting cells and the Vβ chain of the T cell receptor on lymphocytes independently of the sequence of the major histocompatibility complex-loaded antigenic peptide. Interestingly, each superantigen is specifically associated with 1 to 8 of the 24 major Vβ chains that can be found in human T cell receptors (70). This "Vβ profile" may be highly specific. For instance, TSST-1 is associated solely with Vβ2 activation, whereas redundancy between different superantigens sharing the same Vβ profile (e.g., SEB and SEC activate lymphocytes sharing the same Vβ chains) is also observed (69). The number of Vβ chains involved has no known consequences in terms of strength of T cell activation. The Vβ specificity of superantigens could therefore be used as a diagnosis tool: by measuring the differential activation of T cells using flow cytometry, it is possible to formally identify the "signature" of the responsible superantigen according to their Vβ chain, allowing the confirmation of atypical cases and the indirect identification of *S. aureus* (71, 72). T cell activation by superantigens bypasses normal major histocompatibility complex-restricted antigen specificity, leading to activation of up to 20% of total T lymphocytes and thus massive cytokine release (73, 74). The resulting inflammatory pathway does not seem to differ markedly from the septic shock pathway and leads to massive production of IL-1, IL-2, IL-6, tumor necrosis factor, gamma interferon, and various chemokines responsible for the enhancement and dysregulation of the inflammatory response (75). The consequences of this cytokine storm are comparable with those observed in septic shock, with even more intense clinical effects due to the initial intensity of the inflammatory response. Moreover, superantigens upregulate the expression of Toll-like receptors 2 and 4 and thus may enhance the inflammatory response by stimulation of these receptors directly by surface-expressed lipoproteins of *S. aureus* and by endotoxins (lipopolysaccharide) translocated from intestinal flora (76, 77). This "two-hit" hypothesis may explain the observed enhanced severity of bacteremic nmTSS compared with mTSS, in which *S. aureus* is absent from the blood circulation.

Nevertheless, conditions that, *in vivo*, lead to such a massive inflammatory response were largely unknown and have been studied essentially for mTSS. *S. aureus* colonization of the vagina is observed in up to 30% of healthy women (78) and may be influenced by various factors including vaginal microbiota (79, 80). Tampons are thought to favor *S. aureus* growth by elevation of the local oxygen concentration and to enhance TSST-1 production (81–83), but considering that 1% to 6.9% of healthy women carry TSST-1$^+$ *S. aureus* during their menses (84, 85), compared to the by far lower incidence of mTSS, it is obvious that TSST-1 production is not sufficient by itself to induce TSS even in favorable conditions. As discussed above for necrotizing pneumonia, various hypotheses are being studied, including genetic predispositions leading to the absence of antibody against the toxins and/or a specific deficiency in immune responses toward superantigens in a context in which 90% of adults are naturally immunized against TSST-1 (84).

STAPHYLOCOCCAL NECROTIZING FASCIITIS

Necrotizing fasciitis (NF) is a rare and severe presentation of skin and soft tissue infection characterized by extensive necrosis of cutaneous and subcutaneous tissue down to the deep fascia and muscles. This infection is often polymicrobial (type 1 NF) with a combination of Gram-positive cocci, Gram-negative rods, and anaerobes. Type 2 NF is usually monomicrobial, classically involving *S. pyogenes*, and is associated with high mortality (86). Recently, *S. aureus*, and especially the CA-MRSA USA300 lineage, has also been recognized as being responsible for type 2 NF (87).

The clinical description of *S. aureus*-associated NF is difficult since most reports are based on retrospective studies. The presentation is thought to be similar to group A *Streptococcus*-associated cases. The classic initial presentation of NF includes severe pain of the skin out of proportion to physical examination findings. Although some patients appear ill, tenderness, erythema, and warm skin are commonly the only signs of early NF. Shock, fever, and altered mental status typically develop during the first 24 to 48 hours of disease progression but are often absent at presentation (88). Local evolution is extremely severe, with uncontrolled extensive necrosis, but due to the deep-seated localization of the necrosis, the overlying skin may be minimally affected, leading sometimes to delayed diagnosis (88). In many streptococcal cases, signs and symptoms of TSS (i.e., erythroderma) are present, whereas TSS symptoms seem less frequent in staphylococcal NF (87). Therefore, staphylococcal NF should be less severe than the group A *Streptococcus*-associated cases, although to the best of our knowledge, no comparative study exists.

Diagnosis and characterization of staphylococcal NF are thus difficult for several reasons: (i) the diagnosis of

NF can only be made after surgical debridement reveals pathologic findings indicating necrosis involving fascia and muscles. These findings were confirmed in the 14 cases described in Los Angeles, CA, in 2004 (87) but are not always found in other reports. (ii) In cases of polymicrobial NF, especially when group A *Streptococcus* and *S. aureus* are associated, it is almost impossible to determine which bacterium (or both) is the culprit in terms of severity and, in some cases, it appears possible that one bacterium overwhelms another one, leading to misinterpretation of strain-associated virulence. In relation to this, a recent study revealed that of 35 cases with *S. aureus* and/or Gram-negative bacteria as the only cultured pathogens from swab samples, 21 (60%) had beta-hemolytic *Streptococcus*-confirmed infections and 6 (17%) had probable beta-hemolytic *Streptococcus* disease (89). (iii) *S. aureus* is well known for its ability to induce necrotic skin and soft tissue infection, and PVL-producing strains such as USA300 are associated with primary necrotic cutaneous abscesses (9, 90, 91) involving hair follicles (92). Therefore, severe necrotic skin lesions are common with CA-MRSA (93), and in most cases, the disease description does not fulfill the criteria for necrotizing fasciitis and corresponds to common cutaneous abscesses. Because of these difficulties, staphylococcal NF is less well known than the other fulminant infections described above, but some general differences could be underlined: necrotizing pneumonia and TSS usually occur in young and previously healthy individuals and appear to be linked to a specific, but to date hypothetical, complex combination of staphylococcal virulence factors and host predisposition. In the case of NF, patients are older (median age, 50 years), and an underlying condition predisposing nonspecifically to bacterial infection is present in most cases. Hence, diabetes is present in 43 to 53% of cases (87, 94), intravenous drug use in 21%, and immunodepression, HIV infection, and cancer each in 7% of cases (87). Thus, the specific virulence profile of the causative staphylococcal strain remains difficult to ascertain in NF.

BACTEREMIA AND INFECTIVE ENDOCARDITIS

S. aureus bacteremia can occasionally present as a fulminant infection, notably when associated with a deep focus of infection. The most frequently reported deep infectious foci are endovascular foci including infective endocarditis (IE) and central nervous system, bone and joint, soft tissue, and intra-abdominal/pelvic infections. *S. aureus* IE occurs in 5 to 25% of *S. aureus* bacteremia (95–98) and is one of the most rapidly progressive etiologies of IE with the worst outcome, often associated with destruction of cardiac valves (99–101). In a study enrolling 2008 consecutive adult bacteremic patients, meningitis (IE, 59%), persistent bacteremia at 48 hours (IE, 25%) and C-reactive protein of >190 mg/liter (IE, 15%) were independently associated with IE (98). The criteria for severe sepsis or septic shock were met in 30% of *S. aureus* bacteremia without IE (overall in-hospital mortality rate, 24%) and in 51% with IE (overall in-hospital mortality rate, 35%).

Numerous *S. aureus* virulence factors (mostly but not exclusively surface-associated proteins) have been shown, from *in vitro* and/or animal studies, to contribute to the pathogenesis of IE. These include clumping factor A-B, fibronectin-binding protein A-B, collagen-binding protein, SdrD/E, the surface factor promoting resistance to oxidative killing, protein A, coagulase, vWFbp (102–107), and superantigenic toxins such as SEA, SEG, and TSST-1 (108, 109). However, with the exception of SEA, which has been specifically associated with septic shock in the course of bacteremia (110), none of these factors have been specifically associated with fulminant progression and worse outcome in either bacteremia or IE in epidemiological studies. The multifactorial nature of *S. aureus* bacteremia severity is reflected in the observation that higher antibody levels against Hla, delta-toxin, PVL, SEC-1, and PSM-α3 may protect against sepsis in patients with invasive *S. aureus* infections (111). Conversely, certain lineages of *S. aureus*, such as clade 3 of CC30, have been associated with attenuated virulence in hematogenous infections (112), likely because of a stop-codon mutation in the major core-genome-encoded pore-forming toxin (alpha-toxin), reduced transcription of the agr effector RNAIII (113), and the expression of a phenol-soluble modulin variant with attenuated toxic and chemotactic activities (114). Interestingly, there is apparently a higher propensity of low-toxicity isolates to cause bacteremia (115).

THERAPEUTIC ASPECTS OF FULMINANT STAPHYLOCOCCAL INFECTIONS

By definition, fulminant staphylococcal infections are potentially lethal and therefore should be managed according to the guidelines of the sepsis survival campaign, i.e., prompt initiation of bactericidal antibiotics, massive fluid remediation, correction of organ failures, and continuous monitoring of objectives (116). However, despite uncertainties about the pathophysiology,

fulminant staphylococcal diseases may require specific management due to the involvement of staphylococcal exotoxins. These toxins are produced when bacteria reach a high density, owing to the regulation of their production by quorum-sensing systems. In addition, necrotic lesions prevent adequate antibiotic diffusion at the site of infection. For these two reasons, surgical drainage of any accessible lesions should be systematically undertaken. Moreover, therapeutic approaches targeting toxin production are recommended in TSS (117) despite the lack of strong clinical evidence of efficacy. Furthermore, evidence from animal models and limited clinical series indicates that intravenous immunoglobulins, by their ability to broadly neutralize toxins, have a strong potential to limit casualties in fulminant infections (118, 119). Further, to assess the therapeutic potential of toxin-neutralization strategies in fulminant *S. aureus* infections, studies including larger cohorts and utilizing specific antitoxin monoclonal antibodies (46) remain to be performed. Finally, most fulminant *S. aureus* infections are associated with unleashed inflammation, suggesting that adjunctive immunosuppressive therapies might be beneficial to limit mortality and aftereffects. Yet, based on decades of failed trials involving sepsis, the efficacy of specific immuno-interventions in fulminant *S. aureus* infection remains elusive. Importantly, due to fulminant development of the disease conditions, the choice of an appropriate therapeutic regimen should be made immediately—there is no "second chance." In almost all cases this difficult decision has to be made before any bacteriological documentation, emphasizing the need for advanced knowledge of clinical presentations and severity-associated symptoms to avoid potentially deleterious choices, which are always critical, especially because the diseases are so rare.

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