Activation of the Contact System at the Surface of
Fusobacterium necrophorum Represents a Possible Virulence Mechanism in Lemierre’s Syndrome

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Fusobacterium necrophorum causes Lemierre’s syndrome, a serious disease with septic thrombophlebitis of the internal jugular vein, pulmonary involvement, and systemic inflammation. The contact system is a link between inflammation and coagulation, and contact activation by the bacteria could therefore contribute to the abnormal coagulation and inflammation seen in patients with Lemierre’s syndrome. In this study, F. necrophorum was found to bind radiolabeled high-molecular-weight kininogen (HK), a central component of the contact system. Binding was inhibited by the addition of unlabeled HK and domain D5 of HK but not other components of the contact system, indicating a specific interaction mediated through the D5 region. Binding of HK was significantly reduced after pretreatment of the bacteria with trypsin, suggesting that surface proteins are involved in HK binding. Incubation of the bacteria with human plasma resulted in an HK breakdown pattern suggestive of bradykinin release, and bradykinin was also detected in the supernatant. In addition, we show that factor XI (FXI), another component of the contact system, binds to F. necrophorum and that the bound FXI reconstitutes the activated partial thromboplastin time of FXI-deficient plasma. Thrombin activity was detected at the surface of the bacteria following incubation with plasma, indicating that the intrinsic pathway of coagulation is activated at the surface. This activity was completely blocked by inhibitors of the contact system. The combined results show that the contact system is activated at the surface of F. necrophorum, suggesting a pathogenic role for this system in Lemierre’s syndrome.

Fusobacterium necrophorum is an obligate anaerobic Gram-negative rod causing Lemierre’s syndrome, a potentially life-threatening condition that mostly affects previously healthy children and young adults. The disease normally starts in the tonsils and progresses with thrombophlebitis of the internal jugular vein. Septic emboli from the jugular vein can be transported to the lungs, where multilobar pneumonia and pleural empyema are common manifestations, but may also affect other distant sites. The clinical presentation is often dramatic, with high fever, respiratory failure, and even septic shock (4, 31).

The molecular interactions between F. necrophorum and the host largely remain to be examined. Leukotoxin may be a virulence factor and has been shown to promote abscess formation in animal disease, caused by the subspecies necrophorum (7). Tedepalli and coworkers demonstrated leukotoxin activity of four human F. necrophorum subsp. funduliforme isolates (34), but leukotoxin may not be present in all human invasive isolates (18). Friberg and coworkers showed that binding of factor H is important for complement evasion by the bacterium (8). However, the pathogenesis of the distinctive symptoms of Lemierre’s syndrome is unknown. The thrombophlebitis of the internal jugular vein is one of the striking signs and may be due to direct invasion of the vessel wall by the bacteria, causing inflammation and thrombus formation, but procoagulant factors at the surface of the bacteria could also contribute. The contact system is a link between inflammation and coagulation, and contact activation has been demonstrated at the surface of several species of pathogenic bacteria and fungi, such as Candida (1, 2, 14, 16, 20). Inhibition of this system blocks plasma leakage and improves the outcome in animal models of invasive bacterial infection (25, 27).

The contact system (for reviews, see references 6 and 32) is initiated when factor XII (FXII) is bound to a surface. FXII undergoes autoactivation and in turn activates prekallikrein (PK) and FXI, anchored to the surface via high-molecular-weight kininogen (HK). However, PK can also be activated on endothelial surfaces independently of FXII (21) and, in turn, activate FXII, suggesting an alternative route for PK and FXI activation. Activated plasma kallikrein cleaves HK, generating bradykinin. Bradykinin is a potent proinflammatory peptide that causes increased vascular permeability and vasodilatation and is important for plasma leakage in sepsis (24). Activated FXI initiates the intrinsic pathway of coagulation, leading to clot formation. The importance of the contact system for coagulation in vivo has been questioned due to the lack of a bleeding phenotype in individuals lacking FXII. Recent data show that FXII- and FXI-deficient mice are resistant to experimentally induced thrombus formation (5). Thus, the role of the contact system could be to promote a developing thrombus, which may provide a surface for assembly of the contact factors (32). Different surface molecules interact with HK, such as curli, fibrous proteins of Escherichia coli and Salmonella enterica serovar Typhimurium, the M protein of Streptococcus pyogenes (2, 3), gingipains of Porphyromonas gingivalis (29), and lipopolysaccharide (26). Different regions of the HK...
molecule have been shown to bind to various cellular surfaces; domains D3, D4, and D5 of HK bind to platelets or endothelial cells (10–12, 32), and D5 mediates binding and subsequent contact activation at bacterial surfaces (3, 20).

As mentioned, a cardinal symptom of Lemierre’s syndrome is abnormal coagulation and thrombus formation in the jugular vein, and the condition may also include plasma leakage and severe sepsis. Given that contact activation promotes coagulation and increased vascular permeability, we investigated whether the contact system could play a pathogenic role in this severe syndrome, where the underlying mechanisms are poorly understood. The data obtained support this assumption by identifying interactions between F. necrophorum and contact proteins leading to the activation of this procoagulative and proinflammatory system.

MATERIALS AND METHODS

Isolates and growth conditions. Fifteen clinical isolates of F. necrophorum were obtained from the accredited routine diagnostic laboratory of clinical microbiology in Lund, University and Regional Laboratories, Skåne, Sweden. Twelve isolates were from blood of patients with Lemierre’s syndrome, two were derived from peritonsillar abscesses, and one was from a tonsillar swab. In all experiments except one, blood isolate FNB1 from a patient with Lemierre’s syndrome was used. Bacteria were cultured to stationary phase in brain heart infusion broth (BD, Sparks, MD) with 50 μg/ml 1-cysteine, 5 μg/ml hemin, and 0.5 μg/ml vitamin K at 37°C in an anaerobic cabinet (Anaerobic Work Station; Elektrotek). Isolates were further characterized to the subspecies level by sequencing of the gyrA gene. Bacterial DNA was obtained by boiling of 10 bacterial colonies for 5 min in 100 μl of sterile water under vigorous shaking, followed by centrifugation. Five microliters of the supernatant was used as the template in a PCR with the F. necrophorum common primers (15). All reagents except the primers were from Fermentas (Vilnius, Lithuania), and the annealing temperature was 48°C. PCR products were purified with a QIAquick PCR purification kit (Qiagen) according to the instructions of the manufacturer, sequenced using a BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA), and analyzed using an ABI 3100 Genetic Analyzer (Applied Biosystems). Sequences were subjected to Blastn searches, and all sequences showed the highest similarity to F. necrophorum subsp. vulneris.

Serial dilution of washed bacteria of one isolate in phosphate-buffered saline (PBS) was performed, and optical density at 620 nm (OD620) was determined by spectrophotometry. The number of CFU was determined as described above. 

Proteins and plasma. HK, FXII, PK, and FXI were from Kordia, The Netherlands. The synthetic peptide HKH20 (HKHGHGHGKHKNKGKKNGKH) was used. Bacteria were cultured to stationary phase in brain heart infusion broth (BD, Sparks, MD) with 50 μg/ml 1-cysteine, 5 μg/ml hemin, and 0.5 μg/ml vitamin K at 37°C in an anaerobic cabinet (Anaerobic Work Station; Elektrotek). Isolates were further characterized to the subspecies level by sequencing of the gyrA gene. Bacterial DNA was obtained by boiling of 10 bacterial colonies for 5 min in 100 μl of sterile water under vigorous shaking, followed by centrifugation. Five microliters of the supernatant was used as the template in a PCR with the F. necrophorum common primers (15). All reagents except the primers were from Fermentas (Vilnius, Lithuania), and the annealing temperature was 48°C. PCR products were purified with a QIAquick PCR purification kit (Qiagen) according to the instructions of the manufacturer, sequenced using a BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA), and analyzed using an ABI 3100 Genetic Analyzer (Applied Biosystems). Sequences were subjected to Blastn searches, and all sequences showed the highest similarity to F. necrophorum subsp. vulneris. 

For binding experiments, bacteria were washed in PBS containing 0.05% Tween 20 (PBST) and resuspended in the same buffer to different concentrations. One hundred microliters of a 2 × 107/ml bacterial suspension in Tris-buffered saline (TBS) supplemented with 50 μM ZnCl2 was mixed with 100 μl plasma or with 10 μg of FXI or 10 μg of HKH20 in 100 μl TBS and incubated for 30 min at room temperature. For inhibition assays, two test tubes, HKH20 or H-D-Pro-Phe-Arg-CMK to a final concentration of 400 μg/ml was added before plasma. After incubation, the samples were centrifuged and washed in TBS with 50 μM ZnCl2. Bound proteins were eluted with 0.1 M glycine, pH 2, as described previously (9), added to sample buffer containing 2% SDS and 5% mercaptoethanol, and boiled for 3 min.

Bradykinin and FXI were subjected to PAGE using 10% polyacrylamide gels. Plasma diluted 1:100, or kaolin plasma (as described above), served as a control. The protein standard used (Protein Plus) was from Fermentas.

For Western blotting, proteins separated by SDS-PAGE were transferred to a polyvinylidene difluoride membrane (Immobilon-P; Millipore). Membranes were blocked in PBST (PBS plus 0.05% Tween 20) with 5% skim milk for 30 min at 37°C and then incubated for 30 min at 37°C with sheep anti-human HK antiserum AS68 (23) diluted 1:3,000 in blocking buffer. Following three washes in PBST, membranes were incubated for 30 min at 37°C with a peroxidase-conjugated donkey anti-sheep antibody (MP Biomedicals) diluted 1:3,000 in blocking buffer. Bound secondary antibody was detected using SuperSignal West Pico Chemiluminescence substrate (Pierce, Rockford, IL) according to the instructions of the manufacturer and visualized using a Chemidoc camera (Bio-Rad, Milan, Italy).

Bradykinin assay. Bacterial suspensions of 2 × 109/ml in TBS with 50 μM ZnCl2 containing various concentrations of HKH20 or H-D-Pro-Phe-Arg-CMK were incubated with an equal volume of citrated plasma for 15 min at 37°C under rotation. The specific cysteine proteinase E64 at a concentration of 400 μg/ml served as a control peptide, since it should not interfere with the serine proteinases involved in contact activation and has a size similar to that of the other peptides. After incubation, the samples were centrifuged and rapidly resuspended in PBS with 50 μM ZnCl2. Samples were then incubated for 15 min at 37°C, after which they were centrifuged at 14,000 × g and the supernatants were collected. Bradykinin content in the supernatants was determined with an indirect enzyme-linked immunosorbent assay (ELISA) (MARKIT-M-Bradykinin; Dainippon Pharmaceutical Co., Ltd., Osaka, Japan) according to the instructions of the manufacturer.

Clotting time. All clotting time assays were performed using a coagulometer (Amelung, Lemgo, Germany). One hundred microliters of pretreated sample was added to a cuvette and allowed to incubate for 60 s, after which 100 μl of aPTT reagent (aPTT Automatic; Diagnostica Stago) was added. After 60 s, clot formation was initiated by the addition of 100 μl of 30 mM CaCl2. The time to clot formation was measured. All measurements were performed in triplicate. For some experiments, equal volumes of a 2 × 109/ml bacterial suspension in 13 mM sodium citrate buffer, pH 7.4, and citrated plasma were mixed and incubated for 30 min at 37°C. The sample was centrifuged, and the supernatant was collected and subjected to coagulometry. The bacterial pellet was washed in sodium citrate buffer and resuspended in equal volumes of sodium citrate buffer and FXI-deficient plasma, and the sample was subjected to coagulometry. As a control, bacteria pelleted after incubation in FXI-deficient plasma were mixed with FXI-deficient plasma and analyzed.

Thrombin assay. Equal volumes of a 2 × 109/ml bacterial suspension in 50 mM Tris, pH 7.5, with 50 μM ZnCl2 and citrated plasma were incubated for 30 min at 37°C under rotation. HKH20 or H-D-Pro-Phe-Arg-CMK at 400 μg/ml was added to two tubes before plasma. Bacteria were then pelleted, washed twice in Tris with ZnCl2, and resuspended in the same buffer. The chromogenic substrate
S-2238 (Haemochrome Diagnostica, Mölndal, Sweden) was added to a final concentration of 2 mM, and the samples were incubated for 60 min at room temperature. After centrifugation, the supernatants were moved to an ELISA plate and the absorbance at 405 nm was determined.

RESULTS

_F. necrophorum_ binds HK via the D5 region._ The clinical isolate FNB1 of _F. necrophorum_ subsp. _funduliforme_ (this isolate was used throughout this study if not otherwise indicated) was incubated with ^125^I-labeled HK. Binding of HK increased with the bacterial concentration, reaching a maximum of 45% (Fig. 1A). Fifteen clinical isolates of _F. necrophorum_ were then tested for binding of ^125^I-labeled HK. Binding was analyzed at a bacterial concentration of 1 × 10^9^ CFU/ml, and all strains bound HK, with binding ranging from 25 to 50% (Fig. 1B). To test if HK binding to the FNB1 bacteria was displaceable by unlabeled HK, if HK binding shared a binding site with other components of the contact system, and what domain of HK was involved in binding to the bacteria, various inhibition experiments were performed. Binding of radiolabeled HK was already decreasing at a concentration of unlabeled HK of 20 nM and was almost completely blocked at the highest concentrations of unlabeled HK (Fig. 1C). FXII did not inhibit HK binding, indicating that FXII and HK do not share the same binding site on _F. necrophorum_. As expected, PK, which normally binds to cellular surfaces indirectly via HK, did not

![](http://iai.asm.org/)

FIG. 1. ^125^I-labeled HK was incubated with _F. necrophorum_, and binding was determined at different concentrations of bacteria of isolate FNB1 (A) and in 15 different strains (B), 12 from blood isolates (FNB1 to FNB12), 2 from peritonsillar abscesses (FND1 and FND2), and 1 from a tonsillar swab (FNT1). Increasing concentrations of unlabeled HK ( ■ ), LK ( △ ), PK ( ▼ ), or FXII ( ● ) (C), or the D5 peptide HKH20 ( ○ ) or the D3 peptide LDC27 ( ◻ ) (D) were added to the incubation step. In the experiment in panel E, bacteria were pretreated with trypsin prior to the binding assay. The bacterial concentration in panels B, C, and D was 1 × 10^8^/ml, and that in panel E was 1 × 10^9^/ml. The values are the mean ± the standard deviation of three separate experiments.
inhibit HK binding to the bacteria. LK could not inhibit HK binding, despite the fact that LK is similar to HK (Fig. 1C). The difference between the molecules is in the light chain, where LK has no cell binding domain D5. Binding of LK to cellular surfaces is instead mediated mainly by domain D3. The D3 peptide LDC27 could not inhibit HK binding to F. necrophorum, whereas HK could be displaced by the peptide HKH20 from the D5 domain of HK (Fig. 1D), suggesting that binding of HK to the surface of F. necrophorum is mediated mainly by domain D5.

To test if surface proteins are important for the binding of HK to F. necrophorum, the binding of 125I-labeled HK was measured before and after treatment of F. necrophorum with trypsin. As shown in Fig. 1E, binding decreased from over 40% to just above 10% after trypsinization, indicating that binding may be at least partly mediated by exposed proteins.

**HK processing and bradykinin release at the surface of F. necrophorum.** Bradykinin is released when HK, bound to a negatively charged surface, is cleaved by plasma kallikrein. This results in the formation of a specific pattern of HK fragments (33). To test if HK bound to the surface of F. necrophorum is also processed, the clinical isolate FNB1 was incubated with fresh plasma and bound material was eluted and subjected to SDS-PAGE and Western blot analysis to detect HK and breakdown products thereof. Four protein bands were seen, one at 120 kDa corresponding to unprocessed HK, one at 75 kDa, one unique band at 55 kDa, and one band at 45 kDa. Activation of the contact system with kaolin yielded a major protein band at 55 kDa, one at 45 kDa (Fig. 2, lanes 2 and 3), and one band at 75 kDa (Fig. 2, lane 7). Finally, no cleavage generating bradykinin had occurred. The bands at 120 kDa and no band at 55 kDa (Fig. 2, lane 6), indicating that no cleavage generating bradykinin had occurred. The bands at 75 kDa and 45 kDa were similar to the incubation without PK addition, whereas the specific cysteine protease inhibitor E64 served as a control peptide. The values are the mean ± the standard deviation of three separate experiments.

**FXI binds to the bacterial surface and is activated.** F. necrophorum was incubated with 125I-labeled FXI with or without HK. At high bacterial and HK concentrations, up to 75% of 125I-labeled FXI was bound. Without HK, FXI binding reached a maximum of 25% (data not shown). Addition of HKH20 or the plasma kallikrein inhibitor H-D-Pro-Arg-CMK during the plasma incubation step resulted in a dose-dependent inhibition of bradykinin release (Fig. 3), whereas the specific cysteine protease inhibitor E64 at a high concentration had no significant effect.

**FIG. 2.** F. necrophorum was incubated with fresh plasma (lane 5) or buffer (lane 4) for 30 min. After washing, proteins bound to the bacterial surface were eluted and analyzed by Western blotting using a polyclonal anti-HK antibody. The FXII and plasma kallikrein inhibitor H-D-Pro-Phe-Arg-CMK was added during the incubation step in lane 6, and the domain D5 peptide HKH20 was added during the incubation step in lane 7. Untreated plasma (lane 1), plasma treated with kaolin for 30 or 60 s (lanes 2 and 3), and pure HK added to the bacteria (lane 8) served as controls. The values to the right are molecular sizes in kilodaltons.

**FIG. 3.** F. necrophorum was incubated with plasma and resuspended in buffer containing ZnCl2, and bradykinin in the supernatant was measured. Peptide HKH20 derived from domain D5 of HK or the plasma kallikrein/FXII inhibitor H-D-Pro-Arg-CMK was added to the incubation step at increasing concentrations. Cysteine protease inhibitor E64 was added to the incubation step at a very high concentration (400 μg/ml) as a control peptide. The values are the mean ± the standard deviation of three separate experiments.
plasma, restored the aPTT of FXI-deficient plasma (Fig. 4B), suggesting that FXI was absorbed and activated at the bacterial surface. The aPTT of plasma supernatants was prolonged by only about 20% after F. necrophorum preincubation, indicating that minor amounts of late components of the coagulation cascade had been adsorbed to the bacterial surface.

To further investigate the possible activation of the contact system at the bacterial surface, F. necrophorum was incubated with plasma, washed, and then incubated with S-2238, a chromogenic substrate that is cleaved mainly by thrombin. Figure 4C shows that the substrate was cleaved by bacteria preincubated with plasma alone but not when HKH20 or the FXII/plasma kallikrein inhibitor H-D-Pro-Phe-Arg-CMK was present during the plasma incubation step. This indicates that thrombin is activated at the bacterial surface via the intrinsic pathway of coagulation following contact system activation.

**DISCUSSION**

Massive inflammation and disturbed coagulation are distinctive features of Lemi`ere’s syndrome, and the major finding of the present work is that both the procoagulant and proinflammatory branches of the contact system are activated at the surface of F. necrophorum. The levels of HK binding and bradykinin release are comparable to those of other bacterial pathogens known to activate the system, i.e., Staphylococcus aureus, S. pyogenes, E. coli, and Salmonella (2, 20). The finding that trypsin treatment significantly reduced the binding of HK to F. necrophorum indicates that a surface protein may be at least partly responsible for the interaction with HK. It is therefore disturbing that we, despite considerable efforts (involving treatment of the bacterial surface with various proteases or detergents, followed by slot binding or SDS-PAGE and Western blotting probed with 125I-labeled HK), have failed to solubilize and purify a protein with HK-binding activity. There is no obvious explanation for this, but perhaps the three-dimensional structure necessary for HK binding requires that the protein be associated with the bacterial surface.

The starting point for contact activation is when FXII is activated at a negatively charged surface. FXII, in turn, activates plasma kallikrein cleaving of HK to release bradykinin, a potent vasodilator and inducer of plasma leakage. The present work shows that HK bound to the surface of F. necrophorum is cleaved into fragments typical of bradykinin release and that bradykinin indeed is generated following incubation with plasma. These data suggest that contact system activation is responsible for the effect, which is further underlined by the observation that generation of bradykinin was inhibited by the plasma kallikrein/FXII inhibitor H-D-Pro-Phe-Arg-CMK or by a peptide inhibiting binding of HK to the bacterial surface. Other serine proteases than plasma kallikrein, such as FXI, also degrade HK, but the cleavage pattern is different (33). We thus conclude that HK processing and bradykinin release occur via activated plasma kallikrein, which suggests that FXI is also activated.

Active FXII should also trigger the intrinsic pathway of coagulation in the presence of plasma, leading to clot formation at the bacterial surface. However, when tested in the aPTT system, the addition of bacteria to recalcified plasma did not result in clot formation (data not shown). On the other hand, the finding here that FXI binds to F. necrophorum and the detection of FXI at the bacterial surface following plasma incubation (confirmed by an aPTT assay where FXI absorbed from plasma could reconstitute a normal aPTT of FXI-defi-
cient plasma) demonstrate the presence of the proteins required for clotting via the intrinsic pathway. Moreover, thrombin activity was identified at the surface of F. necrophorum after preincubation with plasma, and inhibitors of the contact system blocked this activity. Previous work has demonstrated a fibrin network at the surface of curli-expressing E. coli incubated with plasma in the absence, but not in the presence, of contact inhibitors (28). The present data demonstrate that factors of the intrinsic pathway of coagulation are not only present but also activated at the surface of F. necrophorum, suggesting that fibrin networks may be formed around the bacteria.

In human plasma, FXI circulates in complex with HK, and in the binding assay, the majority of the FXI interacted with the bacterial surface through HK. However, FXI alone also bound to the surface. This was somewhat unexpected, although binding of FXI independently of HK to the surface of human umbilical vein endothelial cells (19) and to S. pyogenes (13), E. coli, and Salmonella (2, 27) has been demonstrated. The significance and mechanism of direct FXI binding to bacteria remain to be determined.

In the aPTT assay of the present study, the plasma supernatants showed almost unaltered aPTT following incubation with F. necrophorum, whereas previous work has demonstrated a hypocoagulatory state of plasma following incubation with isolates of E. coli and S. pyogenes that activate the contact system (13, 14, 27). This discrepancy is explained by the fact that these bacteria, in contrast to F. necrophorum, also efficiently bind and absorb fibrinogen from the plasma, which will affect the final step of both the extrinsic and intrinsic systems. Only 15% of added radiolabeled fibrinogen is bound to the isolate investigated (data not shown), which may not be enough to significantly alter the aPTT of the supernatant. Finally, although as much as 40 to 50% of HK is absorbed by F. necrophorum, it may not alter the aPTT of the supernatant dramatically, since the cascade involves several steps of enhancement and only small amounts are needed to initiate the process.

Contact activation has been demonstrated at the surfaces of several bacterial species not known to induce thrombus formation, suggesting that this is not the only mechanism behind the pathological coagulation in Lemierre’s syndrome. Müller et al. showed that FXII activation is greatly enhanced in the presence of activated platelets releasing negatively charged polyphosphates (22). In Lemierre’s syndrome, the bacteria may migrate through the vessel wall of the internal jugular or tonsillar vein, causing inflammation and platelet activation, as well as initiation of the TF/FVII-driven intrinsic pathway of coagulation. By binding contact factors to its surface and activating the intrinsic pathway, F. necrophorum will further enhance local coagulation.

Activation of the contact system may represent a double-edged sword, on the one hand contributing to host defenses and on the other hand contributing to the pathogenesis of infectious diseases. Local bradykinin production and activation of the intrinsic pathway of coagulation promote inflammation and help to wall off an infection, and the cleavage of HK generates antibacterial peptides (9). However, the enhanced vascular permeability and plasma leakage may also provide bacteria with nutrients, and the fibrin network may protect bacteria against phagocytosis. Massive bradykinin production may cause systemic reactions with low blood pressure and septic shock, and the contact system may also play a role in the development of disseminated intravascular coagulation (DIC).

These symptoms are seen in cases of severe Lemierre’s syndrome, which is also characterized by a slow response to antibiotic therapy and sometimes even treatment failure, although F. necrophorum is fully sensitive to many antibiotics in vitro. A possible explanation could be that bacteria within clots are protected against antibiotic penetration. The formation of clots containing viable bacteria could also explain other typical features of Lemierre’s syndrome, such as the localization of the infection to venous vessel walls and the embolic spread of the infection. Inhibition of the contact system by peptide HKH20 interfering with HK binding and by the FXII/plasma kallikrein inhibitor H-D-Pro-Phe-Arg-CMK has previously been shown to block plasma leakage and fibrin deposition and improve the outcome in animal models of sepsis (25, 27). Also in Lemierre’s syndrome, the contact system may be an attractive therapeutic target to avoid severe sepsis and DIC and increase the efficacy of antibiotic treatment by inhibiting the generation of F. necrophorum-containing thrombi.

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REFERENCES


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ERRATUM

Erratum for Holm et al., Activation of the Contact System at the Surface of 
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Volume 79, no. 8, p. 3284–3290, 2011. Page 3285, column 1, lines 26 and 36: “gyrA” should read “gyrB.”