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Paraoxonases and infectious diseases

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ABSTRACT

The paraoxonases (PON1, PON2 and PON3) are an enzyme family with a high structural homology. All of them have lactonase activity and degrade lipid peroxides in lipoproteins and cells. As such, they play a role in protection against oxidation and inflammation. Infectious diseases are often associated with oxidative stress and an inflammatory response. Infection and inflammation trigger a cascade of reactions in the host, known as the acute-phase response. This response is associated with dramatic changes in serum proteins and lipoproteins, including a decrease in serum PON1 activity. These alterations have clinical consequences for the infected patient, including an increased risk for cardiovascular diseases, and an impaired protection against the formation of antibiotic-resistant bacterial biofilms. Several studies have investigated the value of serum PON1 measurement as a biomarker of the infection process. Low serum PON1 activities are associated with poor survival in patients with severe sepsis. In addition, preliminary studies suggest that serum PON1 concentration and/or enzyme activity may be useful as markers of acute concomitant infection in patients with an indwelling central venous catheter. Investigating the associations between paraoxonases and infectious diseases is a recent, and productive, line of research.

Abstract word count = 191

Keywords: infection; inflammation; lactonases; oxidative stress; paraoxonases; quorum sensing

Abbreviations

AHL	=	*N*-acyl homoserine lactones
APR	=	Acute-phase response
CCL2	=	Chemokine (C–C motif) ligand 2
CRP	=	C-reactive protein
CVC	=	Central venous catheter
HDL	=	High-density lipoproteins
HIV	=	Human immunodeficiency virus
LDL	=	Low-density lipoproteins
PON	=	Paraoxonase
PPAR γ	=	Peroxisome proliferator-activated receptor- γ
SOFA	=	Sequential Organ Failure Assessment

1. Paraoxonases have a role in the innate immune system

The paraoxonases (PON1, PON2 and PON3) are the protein products of a gene family that evolved *via* duplication of a common precursor. They have high structural homology with each other (approximately 60% in the amino acid sequence and 70% in nucleotide) [1] and the three genes are located in adjacent positions of chromosome 7 (7q21.3) [2]. PON1 is a lactonase and ester hydrolase which catalyzes the hydrolysis of thiolactones and some xenobiotics such as organophosphate esters, unsaturated aliphatic esters, aromatic carboxylic esters and carbamates [3-5]. PON2 and PON3 do not degrade xenobiotics, but have lactonase activity [6]. All three PON enzymes degrade lipid peroxides in low-density lipoproteins (LDL) and high-density lipoproteins (HDL) [6]. In addition, PON2 reduces intracellular oxidative stress and decreases apoptosis [7]. In humans, *PON1* and *PON3* genes are mainly expressed in the kidney and liver, and the enzymes are found in blood bound to HDL particles [3,8-10]. Conversely, the *PON2* gene expression is almost ubiquitous, and its protein product is an intracellular enzyme that is not found in the circulation [11].

Paraoxonases are polymorphic enzymes. Playfer *et al.* [12] were the first to report that PON1 activity was determined by a single autosomal locus with two possible alleles. In 1983, Eckerson *et al.* [13] reported that two isoenzymes (termed Q and R) differed in a particular property: the R allozyme having a greater ability to hydrolyze paraoxon than the Q allozyme. Later, this group sequenced the coding region of PON1, and two polymorphic sites were identified: Leu/Met in position 55 (polymorphism $PON1_{55}$) and Arg/Gln in position 192 (polymorphism $PON1_{192}$). Polymorphism $PON1_{192}$ clearly correlated with phenotypes Q and R described above: individuals with the Gln variant at position 192 belonging to the phenotype Q, while those with the Arg at position 192 exhibited the phenotype R [14]. In 1997, Blatter-Garin *et al.* [15] studied the influence of the $PON1_{55}$ genotype on the enzyme's activity and concentration in serum of diabetic patients, and observed significant differences with respect to the different isoforms i.e. individuals who had a Leu at position 55 (L isoform) had higher concentrations of PON1 than carriers of a Met (M isoform), and these increases in paraoxonase concentrations correlated with parallel increases in enzyme activity. More recently, several other polymorphic sites in the promoter region of the human *PON1* gene have been described at –107, –126, –162, –832, –909, –1076, and –1741 positions [16,17]. Among these polymorphisms, T (–107) C appears to be associated with variations in concentration and activity of PON1 in serum. Indeed, the effect of $PON1_{55}$

on serum PON1 concentrations appears to be due to $PON1_{-107}$ polymorphism, with which it is in strong linkage disequilibrium. More recent studies demonstrated that PON2 and PON3 are also polymorphic enzymes, and that $PON2_{148}$, $PON2_{311}$, and six different *PON3* polymorphisms are in linkage disequilibrium, and co-segregate together [18]. The effects on the function of these enzymes are similar [18-20] (Figure 1).

PON1 degrades oxidized lipids in LDL and HDL and inhibits the synthesis of the pro-inflammatory chemokine (C–C motif) ligand 2 (CCL2) [21]. Watson *et al*. [22] demonstrated that treatment of oxidized LDL with purified PON1 significantly reduces the ability of this lipoprotein to induce interactions between monocyte and endothelial cells, and that this effect was associated with a decrease in the amount of oxidized phospholipids present in the LDL particles (especially oxidized 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphoryl choline). These authors suggested that the physiological function of PON1 was to protect against induction of inflammatory responses by hydrolyzing the pro-inflammatory oxidized phospholipids in LDL. A subsequent study [23] demonstrated that, in addition to LDL particles, PON1 also protects HDL from oxidation. These *in vitro* experiments were confirmed in experimental animals when Shih *et al.* [24] reported that HDL particles obtained from mice deficient of the *PON1* gene lacked the ability to protect LDL from peroxidation. The same research group later showed that mice double-deficient for *PON1* and *apolipoprotein E* genes have higher levels of *in vivo* lipid peroxidation products than the animals that were deficient in apolipoprotein-E alone [25]. Schweikert *et al.* [26] showed that PON2 and PON3 protect several human cell lines against *Pseudomonas aeruginosa* infection. In addition, other investigators found that PON2-deficient mice have a higher sensitivity to bacterial infections than wild-type mice [27,28]. Several studies suggest that PON1 participates in the protection conferred by HDL against different infectious agents, including bacteria [29,30] and viruses [31,32]. Overall, these results indicate that the enzyme proteins of the PON family can be considered part of the innate immunity system [33].

2. Paraoxonases are potential anti-biofilm agents

The extensive use of catheters and the implantation of artificial prostheses is one of the greatest progresses in Medicine. However, an important side effect of these maneuvers is the susceptibility to infections which are difficult to treat because bacteria develop biofilms at the site of the intervention, and are becoming resistant to antibiotics currently available. Biofilms are evolutionary adaptations by bacteria which enables

them to survive in hostile environments, and to colonize new ecological niches [34,35]. A biofilm is an aggregation of bacteria, often composed of millions of microorganisms, embedded within a self-generated matrix composed of extracellular proteins, DNA, and polysaccharides. Bacteria present in biofilms have high resistance to antimicrobial agents. Polysaccharides in biofilms are composed, mainly, of *O*- or *N*- acylated monosaccharides. The most common extracellular polysaccharides are poly-ß-1,6-*N*-acetylglucosamine, cellulose, and alginate. The bacteria within the biofilms can develop specialized and coordinated phenotypes. These include antibiotic resistance and nutrient utilization together with expression of virulence factors and surface molecules [36-41]. A major concept in bacterial biofilm formation is that of quorum sensing. This phenomenon is defined as the coordination of the bacterial behavior via the accumulation of signaling molecules. Quorum sensing relies on the phenomenon of signaling molecule concentrations reaching a critical threshold resulting in the modulation of certain target genes triggering biofilm formation [42]. In Gram-negative bacteria, *N*-acyl homoserine lactones (AHL) have been identified as the major signaling molecules in this communication system [43,44]. In spite the high number of Gram-negative species, only a few varieties of AHL are involved in quorum sensing (Table 1). The first reported quorum sensing AHL was identified from *Vibrio fischeri* as *N*-(3'-oxohexanoyl)-L-homoserine lactone (3-oxo-C_6-AHL) that is synthesized by the LuxI protein [45,46]. Probably the most well documented bacteria in relation to quorum sensing is *P. aeruginosa*. This bacterium colonizes the lungs of patients with cystic fibrosis, and forms a biofilm on the epithelial cells of the airways [47]. Chronic infection by *P. aeruginosa* results in progressive lung damage and, eventually, death from respiratory failure. Because of the architecture of the biofilm structures, antibiotic treatment is very ineffective [36,48]. A scheme of biofilm formation is shown in Figure 2, and an excellent Review on biofilm characteristics has been published recently [49].

P. aeruginosa biofilm formation is initiated by two quorum-sensing AHL, *N*-(3'-oxododecanoyl)-L-homoserine lactone (3-oxo-C_{12}-AHL) and *N*-butyryl-L-homoserine lactone (C_4-AHL) [50,51]. These molecules are synthesized by LuxI-like enzymes and recognized by LuxR-like receptors. The lactone 3-oxo-C_{12}-AHL is synthesized by LasI and detected by LasR, while C_4-AHL is synthesized by RhlI and detected by Rh1R [52-54]. The current consensus is that Gram-negative bacteria use various AHLs to regulate the molecular mechanisms involved in biofilms and other adaptive responses. For example, metalloprotease and serine protease production in *Aeromonas hydrophila* are

regulated by *N*-butanoyl-AHL, bacterial conjugation in *Agrobacterium tumefaciens* is regulated by 3-oxo-C_8-AHL, 1-carbapen-2-em-3-carboxylic acid β-lactam synthesis by *Erwinia carotovora* is regulated by 3-oxo-C_6-AHL, and aggregation in *Rhodobacter sphaeroides* is regulated by 7,8-*cis*-*N*-(tetradecanoyl)-AHL [55].

Considerable evidence suggests that the PON enzyme family plays an important role against biofilm formation in Gram-negative bacteria infection. Epithelial cells and resident macrophages are important defense mechanisms of the lungs against external toxic agents and microorganisms. PONs are strongly expressed in lung epithelial cells and, as stated above, they are mainly lactonases [56,57]. Thus, it seems logical to infer that PONs are able to hydrolyze AHL and interrupt quorum sensing signals. This hypothesis has been demonstrated *in vitro* by investigators [58-60] who found that lung epithelial cells inactivate 3-oxo-C_{12}-AHL, and that this capacity is present in cell membranes but is not secreted into the airway fluid. Subsequent studies in cultured lung epithelial cells exposed to 3-oxo-C_{12}-AHL demonstrated that a lactonase was responsible for these outcomes [61]. This research group also reported that wild type mouse serum, rich in PON1, degraded 3-oxo-C_{12}-AHL and decreased *P. aeruginosa* biofilm formation, and that this capacity was lost when serum from PON1-deficient mice was employed in the *in vitro* experiments. Further, adding back purified PON1 to serum from PON1-deficient mice restored the ability to degrade 3-oxo-C_{12}-AHL and inhibited biofilm growth [61]. These data demonstrated that PON1 efficiently degrades 3-oxo-C_{12}-AHL and reduces the growth of bacterial biofilms. Further studies showed that PON2 and PON3 are also able to degrade 3-oxo-C_{12}-AHL, with PON2 being the more efficient in this function [62-65]. These findings have been confirmed by other investigators: Stoltz *et al.* [27] used a quorum sensing reporter strain termed PAO1-qsc-102-lacZ that produces β-galactosidase in response to quorum sensing signals. They showed that β-galactosidase concentrations were 2.5 times higher in bacteria harvested from PON2-deficient mice lung epithelia compared to controls. In addition, 3-oxo-C_{12}-AHL has been shown to down-regulate PON2 expression in cultured airway epithelial cells [43]. Ma *et al.* [66] reported that cloning human PON1, PON2 or PON3 into *P. aeruginosa* results in an inhibition of biofilm formation, and decreased antibiotic resistance; a phenomenon that was reversed by adding anti-PON antibodies to the culture media. These results demonstrate that the hydrolytic activity of PON1 and PON2 is an important defense mechanism for the control of *P. aeruginosa* quorum

sensing. More recently, an experimental model in *Drosophila melanogaster* has been employed to investigate the role of the PON family in protecting against biofilm formation. Insects do not have PON, and human PON1 transgenic flies had an increased survival following infection with *P. aeruginosa* and *Serratia marcescens*, another AHL-sensing bacterium [67]. A recent interesting study showed that macrophages infected with *P. aeruginosa* and treated with pioglitazone (an agonist of the peroxisome proliferator-activated receptor-γ; PPAR γ) showed increased phagocytosis and bacterial clearance [68]. PPARγ is known to induce PON2 gene and protein expression in macrophages [69,70].

3. Alterations in serum PON levels and activity in infectious diseases and the acute phase response

Infectious diseases are often associated with oxidative stress and an inflammatory response [71]. Infection and inflammation trigger a cascade of reactions in the host, known as the acute-phase response (APR). This response is associated with changes in lipoproteins [72,73], especially in HDL particles. During the APR, there is a reduction in the levels of proteins involved in HDL-mediated reverse cholesterol transport and those that inhibit plasma lipid oxidation. These include lecithin:cholesterol acyltransferase, cholesterol ester transfer protein, phospholipid transfer protein, apolipoprotein A-I, and PON1. Moreover, the lipid composition of the HDL particles during the APR is altered e.g. a depletion in cholesterol esters and an enrichment in free cholesterol, triglycerides, and free fatty acids [74]. The levels of apolipoprotein J and serum amyloid A increase several fold in acute-phase HDL [75]. Overall, these changes cause HDL particles to lose some of their anti-atherogenic and anti-inflammatory properties, and may even become pro-atherogenic and pro-inflammatory. This process is schematized in Figure 3. In summary, infectious diseases are often associated with decreased serum PON1 enzyme activity and/or concentration.

Many studies have suggested an association between bacterial infections and an increased risk of cardiovascular diseases. This phenomenon has been studied particularly in the case of *Helicobacter pylori* infections [71, 76-78]. Some authors have investigated the possibility that these complications are related to alterations in PON1. Aslan *et al.* [79] reported a significant decrease in serum PON1 activity and an increase in the levels of lipid hydroperoxides in *H. pylori*-infected patients compared to non-infected subjects (n=56 *vs.* 43). They observed a significant relationship between PON1 and HDL-cholesterol concentrations in the overall study group. Akbas *et al.* [80]

confirmed these results in a further study which also evaluated carotid-intima thickness (a surrogate marker of atherosclerosis). However, they did not note any significant association between this parameter and serum PON1 activity. Further, results in patients with *Brucella* infection are contradictory. One study reported decreased serum PON1 activity together with an atherogenic lipid profile and increased concentrations of pro-inflammatory cytokines [81]. However, another study found a decreased oxidant status and unmodified serum PON1 activity in similar patients [82]. Data relating other bacterial infections with changes in serum PON1 activity are scarce. One study found decreased enzyme activity and increased lipid hydroperoxides in patients with tuberculosis [83], and another reported similar data in patients with leptospirosis [84]. Infection with the *Protists* of the *Leishmania* genus has also been reported to be associated with decreased serum PON1 activity e.g. a pro-atherogenic lipid profile and increased concentrations of pro-inflammatory cytokines [85].

Sepsis and septic shock are important causes of morbidity and mortality in intensive care units. In these patients, dramatic alterations in serum PON1 activity and lipid profile have been reported. Circulating levels of HDL-cholesterol are reduced, and the magnitude of this reduction is positively correlated with the severity of the disease. These patients have decreased serum PON1, decreased platelet-activating factor acetylhydrolase, increased oxidative stress, increased levels of several acute-phase proteins (including serum amyloid A and secretory phospholipase A2), increased concentrations of endothelial cell adhesion molecules, and increased pro-inflammatory cytokines [86-87]. Novak *et al.* [89] reported that serum PON1 activities in patients with severe sepsis were almost 50% lower than those observed in the control group, and were normalized following the patients' recovery. They also observed a positive correlation between serum PON1 activity and HDL-cholesterol, and a negative correlation with the serum concentration of the APR-related C-reactive protein. In a further study, this group described reduced catalase activity and increased pro-inflammatory cytokines in patients with sepsis; levels that were associated with the alterations in serum PON1 activity and HDL-cholesterol [90]. Our research group designed a longitudinal, prospective, observational study with 15 patients with sepsis who were studied at baseline and on days 1, 2, 5, 7 and 10 of their stay in Intensive Care [91]. We measured serum PON1 and PON3 concentrations, PON1 activity, serum CCL2 concentrations, and several standard biochemical and hematological parameters in all the patients. The results indicated that CCL2 was increased and PON1 activity

was decreased at baseline in patients compared with controls. Further, the CCL2 concentrations were significantly decreased with the resolution of sepsis, and this decrease was especially important during the first 5 days of hospitalization. We found that the PON-related variables were slightly increased, and that PON1 activity had a significant and inverse correlation with the Sequential Organ Failure Assessment (SOFA) score at the end of hospitalization. The SOFA score is an estimation of the extent of organ function (or failure) [92], and our results suggest that serum PON1 activity measurement can be seen as an index of positive sepsis resolution. Other studies with greater numbers of patients confirmed that low serum PON1 activities are associated with poor survival in patients with severe sepsis [93,94].

Alterations in the PON1 status are also observed in viral infections. Patients with human immunodeficiency virus (HIV) infection often develop pro-atherogenic metabolic alterations which can be explained by the infection itself, or by the secondary effects of antiretroviral therapies [95,96]. HDL-cholesterol is decreased in HIV-infected patients [97,98], and the higher HDL concentrations the better is the disease-course in HIV-infected patients undergoing antiretroviral treatment [99]. We studied 212 patients with HIV infection and 409 healthy subjects, and found that serum PON1 activity was decreased and its concentration was increased in patients relative to control individuals. Higher PON1 activities were associated with higher CD4+ T lymphocyte counts which indicated a better immunological status [100]. Further studies from our group identified high serum PON3 concentrations in HIV-infected patients which were negatively associated with the circulating levels of oxidized LDL [101]. Also, we identified several haplotypes in the *PON1-2-3* genetic cluster that were related to the patients' metabolic disturbances, atherosclerosis and immunologic outcomes [32]. However, we did not observe any significant relationship between serum PON1 activity (or concentration) and the extent of the atherosclerosis lesion [102-104]. A proteomic study by Siegel *et al.* [105] recently reported decreased levels of PON1 in HDL from HIV patients relative to HDL from uninfected controls; the levels being irrespective of treatment. In contradiction of our earlier report, they also observed decreased levels of PON3.

Viral hepatitis is also associated with changes in PON1 status. Patients with hepatitis B infection were observed to have low serum PON1 activities as well as high lipid hydroperoxide levels and total oxidant status [31,106]. In addition, maternal chronic hepatitis B virus infection was shown to be related to low serum PON1 activities in newborns [107]. Also in relation to hepatitis C, one study reported that the

frequency of phenotype R of the *PON1*$_{192}$ gene polymorphism is higher in infected patients than in normal individuals [108] while another study reported low activities of the enzyme in these patients [109]. Finally, patients with dengue infection were observed to have decreased serum PON1 activities, and increased levels of oxidative stress [110].

4. Paraoxonases and hospital acquired infections

Hospitalized patients are at high risk of infection, mainly associated with the use of catheters or prostheses. Our research group has paid special attention to the infections associated with central venous catheters (CVC) and urinary catheters. The National Healthcare Safety Network defines a CVC as "an intravascular catheter terminating in or near the heart or one of the great vessels, used for the infusion, blood collection or hemodynamic monitoring". Large vessels are the aorta, pulmonary artery, superior vena cava, inferior vena cava, brachiocephalic veins, internal jugular veins, subclavian veins, external iliac vein, common iliac veins, femoral veins and, in newborns, the umbilical artery or vein [111]. Risk factors for CVC-related infections are classified as intrinsic (related to the host) and extrinsic (related to the type of catheter, insertion procedures, or maintenance). The most significant intrinsic risk factors were observed to be extreme age (very young or very old), chronic illnesses, malnutrition, administration of parenteral nutrition, loss of skin integrity (burns), immunodeficiency, neutropenia, and bone marrow transplant. The extrinsic risks of infection vary with the type of vascular catheter. For CVC these factors are the following: femoral insertion as opposed to the jugular or subclavian insertions, parenteral nutrition, insertion with suboptimal barrier measures, repeated catheterization in the course of the same hospitalization, repeated attempts to catheterize at in the same insertion site, to have a septic focus, long duration of catheterization, multi-lumen catheter use, insertion in intensive care or emergency departments, and microbial contamination of the connection or insertion point [112-114]. Catheter-associated bloodstream bacteremia may occur *via* microorganism colonization of the catheter (either extra-luminal or intra-luminal). Intra-luminal contamination results in bacterial entry into the patients' circulatory system via the infusion device, or due to manipulation of the connections of the infusion equipment. In extra-luminal contamination, microorganisms migrate into the bloodstream from the insertion site on the skin along the outer surface of the catheter. Infrequently, microorganisms may adhere directly to the catheter tip after circulating in the blood from a focus of distant bacteremia and subsequently, although the primary focus

contamination may be resolved, the contaminated catheter tip becomes a new source of secondary bacteremia [115-117]. The main causes of CVC infection are depicted in Figure 4. After insertion, plasma proteins begin to adhere to form a fibrin layer around the catheter [117]. When microorganisms reach the catheter they adhere irreversibly to the surface, producing quorum sensing signals and biofilm formation. Dispersion of biofilms causes blood-borne dissemination of the bacteria [118,119].

Treatment of CVC infection involves decision-making regarding catheter removal and administration of antibiotics. However, the diagnosis of bacteremia is often complicated by non-specific symptoms such as fever, chills, and hypotension [120]. Hence, identifying efficient biomarkers for the diagnosis of bloodstream infections in patients with an indwelling CVC becomes essential, and is an active line of research. Several studies have proposed the measurement of C-reactive protein (CRP) or procalcitonin as useful markers of sepsis. However, their usefulness depends on the clinical situation which, to date, remains an unresolved problem [121]. We recently conducted a prospective study with 114 patients who had had an indwelling CVC removed because of infection, or because it was no longer needed (according to the criteria of the attending physician). The aim of the study was to evaluate alterations in PON1 levels in the circulation of these patients and to investigate the potential utility of this parameter as a biomarker for the diagnosis of infection. We observed that patients with a CVC had higher CCL2, CRP and procalcitonin concentrations than the control group, and lower PON1 activities and, perhaps more importantly, there were no significant differences in PON1 concentrations. The degree of alteration correlated well with the severity of the infection. We also found that the accuracy of PON1 measurement (concentration and/or activity) in the diagnosis of an acute concomitant infection was significantly higher to that of CCL2 and the classical biochemical markers of infection (CRP and procalcitonin) [122]. In another study, we sought to characterize the alterations of PON1 and CCL2 levels in the circulation of elderly hospitalized patients who had an indwelling urinary catheter. We prospectively recruited a total of 142 patients ≥60 years of age. As in patients with a CVC, we observed that patients with an indwelling urinary catheter had higher concentrations of CCl2, CRP and procalcitonin than did the control group, and lower PON1 activities. In this situation as well there were no significant differences in PON1 concentrations. However, the diagnostic accuracy (i.e. the ability to discriminate between patients with and without an acute concomitant infection; or those with and without a catheter-

associated bacteriuria was low in all the investigated variables, and with a high degree of overlapping between patient groups [123].

5. Conclusion

Currently, most investigators agree that paraoxonases play important roles in the innate immune system, due to their antioxidant properties and their ability to degrade AHL (molecules involved in bacterial quorum sensing). Most studies to date agree that infectious processes occur in association with low serum PON1 activities. This finding suggests that PON1 may play a role in the pathophysiology of infection and the associated inflammatory reaction. The possibility that determining the level of serum PON1 activity may constitute an efficient biomarker of infection is an active line of research.

Conflict of interest

The authors confirm that there is no conflict of interest in relation to this article and its content.

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Figure legends

Fig. 1. Polymorphisms in the promoter and coding regions of paraoxonases (PON) 1, 2, and 3

Fig. 2. Formation of a biofilm begins with the attachment of the early colonizer planktonic bacteria to an organic or inorganic surface. These cells adhere to the surface *via* van der Waals forces and using cell adhesion structures such as pili and fimbriae. This primal colony begins cell division and produces the extracellular matrix that defines a biofilm. Some microorganisms cannot attach to the surface on their own but can anchor themselves to the matrix or to earlier colonists. It is at this stage that the number of cells becomes sufficient for the synthesis of quorum sensing molecules, such as N-acyl homoserine lactones. Once colonization has begun, the biofilm grows through a combination of recruitment, multiplication, and specialization of cell function. Finally, some bacteria can abandon the biofilm to begin colonization of a new niche.

Fig. 3. Schematic representation of enzymatic changes occurring within high-density lipoproteins (HDL) as a result of the acute-phase response. Apolipoprotein A-1 and antioxidant enzymes are replaced by inflammatory proteins, rendering HDL less protective and, in some cases, pro-inflammatory. These modified HDL particles are severely depleted of PON1.
A-I: apolipoprotein A-I; A-II: apolipoprotein A-II; CETP: cholesteryl ester transfer protein; J: apolipoprotein J; LCAT: lecithin:cholesterol acyltransferase; PAF-AH: platelet activating factor acyl hydrolase; PLTP: phospholipid transfer protein; PON1: paraoxonase-1; SAA: serum amyloid A; sPLA2: secretory non-pancreatic phospholipase A2.

Fig. 4. Potential sources of infection related to intravascular catheter: the flora of the skin, contamination of the catheter hub and lumen, fluid infusion and hematogenous colonization of the catheter from a focus of distant bacteremia. HCW: Healthcare worker.

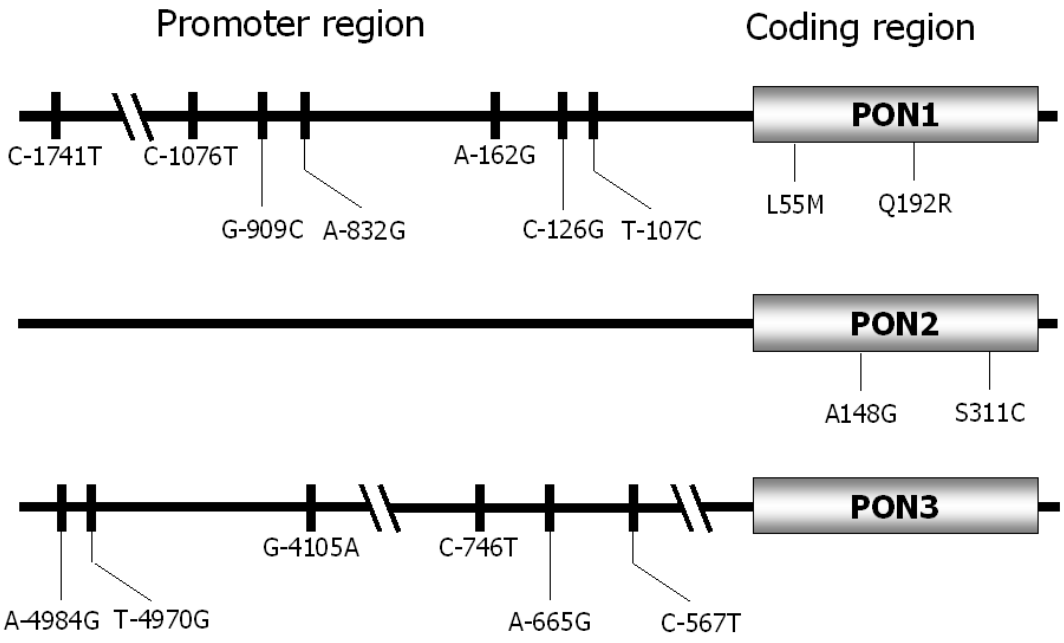


Fig. 1

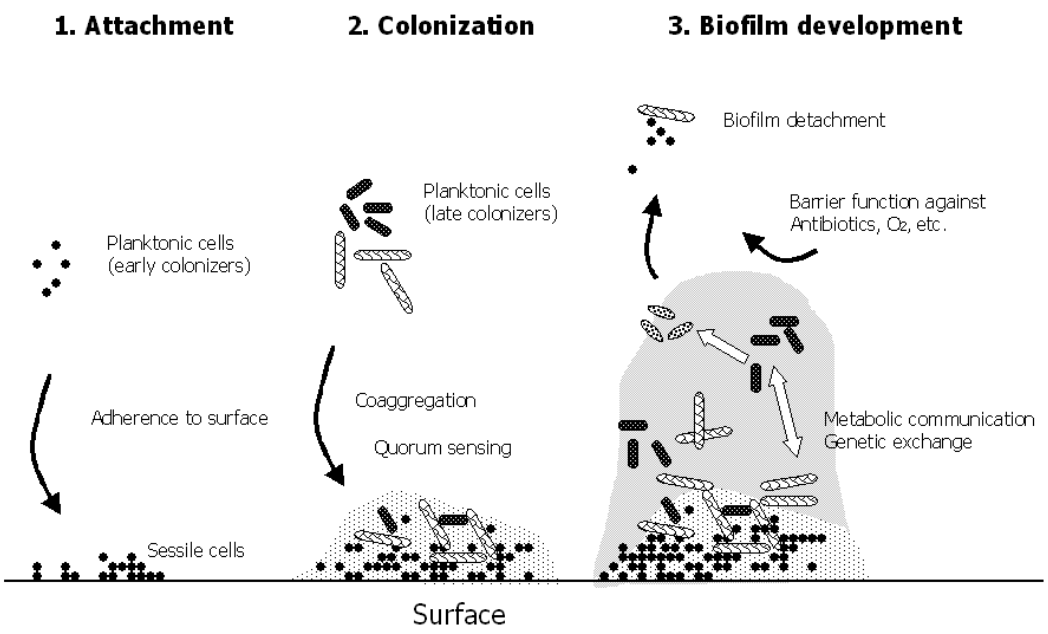


Fig. 2

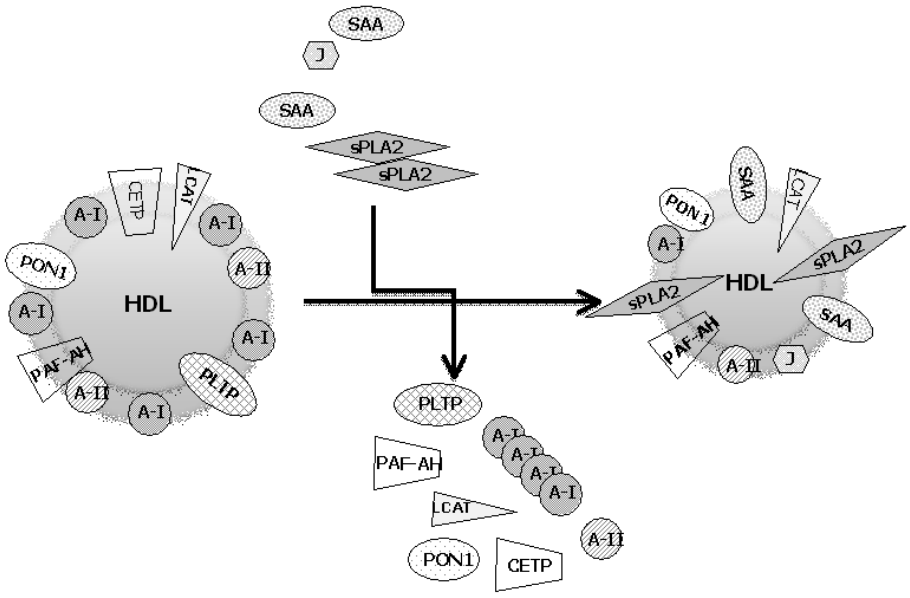


Fig. 3

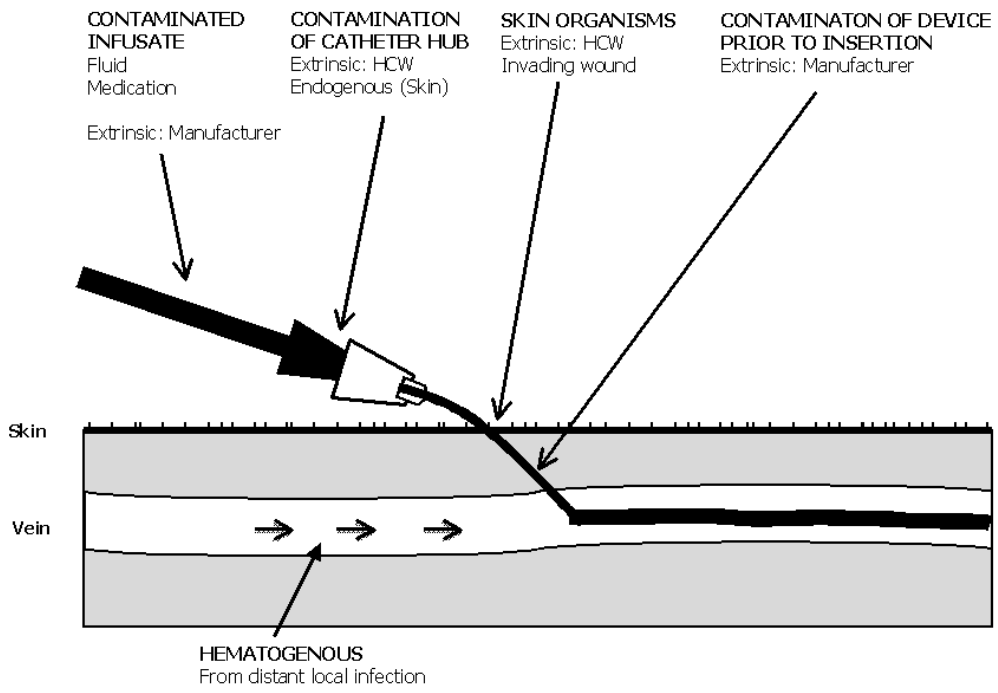
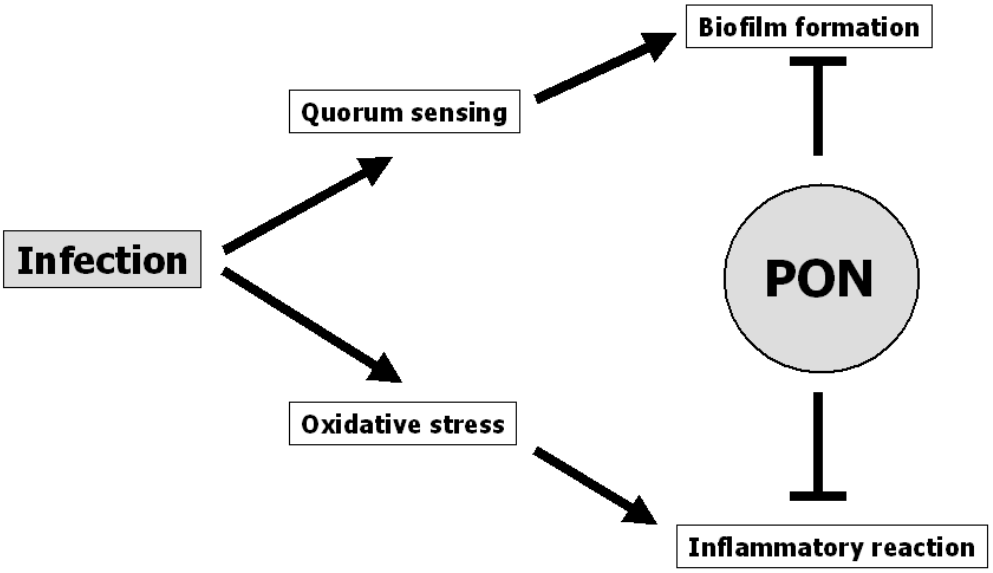


Fig. 4

Table 1. Quorum sensing-related acyl homoserine lactones (AHL) employed by several Gram-negative bacteria.

Organism	**Molecule**
Aeromonas hydrophila	*N*-butanoyl-AHL
Aeromonas salmonicida	*N*-butanoyl-AHL
Agrobacterium tumefaciens	*N*-(3-oxo-C_8)-AHL
Burkholderia cepacia	*N*-C_8-AHL
Erwinia carotovora	*N*-(3-oxo-C_6)-AHL
Pseudomonas aeruginosa	*N*-(3-oxo-C_{12})-AHL
	N-C_4-AHL
Pseudomonas chlororaphis	*N*-C_6-AHL
Rhodobacter spheroides	7,8-*cis*-*N*-C_{14}-AHL
Vibrio fischeri	3-oxo-C_6-AHL



Graphical abstract

Highlights

- The paraoxonases are antioxidant enzymes that degrade lipid peroxides
- Infectious diseases are associated with oxidative stress and inflammation
- Serum paraoxonase activity is often decreased in infectious diseases
- The implication of paraoxonase alterations in infection is an active line of research