

# Acquired Disorders of Phagocyte Function Complicating Medical and Surgical Illnesses

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There is evidence that acquired dysfunction of neutrophils, monocytes, or macrophages is an important cause of infection in patients with diabetes mellitus, renal or hepatic failure, alcoholism, autoimmune diseases, influenza or human immunodeficiency virus infection, burns, and trauma. Distinguishable mechanisms of acquired phagocyte dysfunction include inhibitory effects of metabolic disturbances (e.g., hyperglycemia, uremia), chemical toxins (e.g., ethanol), viral proteins on phagocyte activation, and pathologic activation of phagocytes in the circulation (e.g., after hemodialysis, burns, or cardiopulmonary bypass). Although the burden of morbidity and mortality resulting from acquired phagocyte dysfunction appears to be vast, research in this area has been hampered by the complexity of the underlying illnesses and by limitations of laboratory assays and clinical study methodology. Given the advent of improved assays of phagocyte functions and treatments that can enhance these functions, there is a pressing need for more prospective studies of acquired phagocyte dysfunction.

A wide variety of common medical and surgical illnesses are associated with an increased risk of infection with bacterial or fungal organisms that are characteristically contained by phagocytes (table 1). Although these illnesses are complex and diverse clinical features are identified as risk factors for infection (table 1), all are associated with acquired phagocyte dysfunction (table 2). This review will summarize the evidence that acquired phagocyte dysfunction is an important contributing cause for the infections that complicate these

disorders. Although the mechanisms of phagocyte dysfunction vary widely, certain general themes emerge.

## DIABETES MELLITUS

Infections pose a serious threat to patients with diabetes and account for up to 22% of deaths [1, 2]. Hyperglycemia is associated both with an increased risk of infection and abnormalities in neutrophil function [3, 4]. Excess use of nicotinamide adenine dinucleotide phosphate (NADPH) in the aldose reductase pathway [5] may account for impaired phagocyte NADPH oxidase activity in patients with diabetes mellitus. In the neutrophils of patients with diabetes, phagocytosis, intracellular killing of bacteria, or both are also depressed [3, 6, 7]. Improved glucose control and treatment of patients with diabetes with aldose reductase inhibitors have been reported to increase respiratory burst and phagocytic activities of neutrophils in persons with diabetes [7–10]. In a double-blind, placebo-controlled study, granulocyte colony-stimulating factor (G-CSF) treatment increased neutrophil superoxide pro-

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**Table 1. Acquired disorders of phagocyte function and characteristics of frequently associated infections.**

Condition	Primary site of infection	Pathogen	Cause of death related to infection, %	Clinical factors predisposing patient to infection
Diabetes mellitus	Lung, urinary tract, soft tissue, bone, catheter-related, liver, eye	<i>Staphylococcus aureus</i> , <i>Pseudomonas</i> species, <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , anaerobes, and <i>Candida</i> , <i>Mucor</i> , and <i>Rhizopus</i> species	22	Hyperglycemia, total parenteral nutrition, malnutrition, skin ulcers, urinary catheterization
Renal failure	Dialysis catheter, peritoneum, <sup>a</sup> lung, blood, urinary tract	<i>S. aureus</i> , aerobic gram-negative bacteria	13–24 <sup>b</sup>	Diabetes mellitus, peripheral vascular disease, dialysis with cuprophane membranes
Alcoholism	Lung, blood, heart valves, meninges	<i>Streptococcus pneumoniae</i> , <i>S. aureus</i> , anaerobes, <i>Bartonella quintana</i> , <i>Listeria monocytogenes</i> , <i>Actinomyces</i> species, <i>Candida</i> species, <i>Mycobacterium tuberculosis</i>	See text	Hemochromatosis
Cirrhosis	Urinary tract, lung, peritoneum, soft tissue, blood	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Escherichia coli</i> , <i>K. pneumoniae</i> , <i>Aeromonas</i> species, <i>Vibrio</i> species	5–30 <sup>c</sup>	Urinary catheterization, instrumentation, complement deficiency
SLE	Blood, lung	<i>S. aureus</i> , gram-negative bacteria, <i>Mycobacterium tuberculosis</i> , opportunistic organisms	33	Immunosuppressive drugs, renal failure, exacerbation of SLE
Influenza virus	Lung, trachea, ear, meninges, blood	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Neisseria meningitidis</i>	See text	Advanced age, not influenza vaccinated
HIV	Lung, blood, catheter related	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida</i> species	See text	Injection drug use, low CD4 count, no antiretroviral therapy
Burns	Lung, blood, urinary tract, wound	<i>S. aureus</i> , <i>Pseudomonas</i> species, aerobic gram-negative bacteria, <i>Candida</i> species, herpes simplex virus	54 <sup>d</sup>	Burn size >40% body surface area, extremely young or advanced ages
Trauma	Lung, blood, wound, urinary tract	Aerobic gram-negative bacteria, <i>S. aureus</i>	See text	Advanced age
Cardiopulmonary bypass	Wound, lung, urinary tract	<i>S. epidermidis</i> , <i>S. aureus</i> , aerobic-gram negative bacteria, <i>Candida</i> species	See text	Prolonged bypass time, diabetes mellitus

**NOTE.** SLE, systemic lupus erythematosus.

<sup>a</sup> In patients undergoing peritoneal dialysis.

<sup>b</sup> Patients with end-stage renal disease who are undergoing hemodialysis.

<sup>c</sup> In-hospital mortality.

<sup>d</sup> Burn size grades III and IV.

**Table 2. Differential features of altered neutrophil and monocyte function in medical and surgical illnesses.**

Illness	Adherence	Chemotaxis	Respiratory burst	Phagocytosis	Bacterial killing	Macrophage FcR clearance	Miscellaneous
Diabetes mellitus	Increase	Both <sup>a</sup>	Decrease	Decrease	Decrease	—	NADPH decrease, cytosolicCa <sup>++</sup> increase
Renal failure	Both	—	Both	Decrease	—	Decrease	Cytosolic Ca <sup>++</sup> increase
Alcohol <sup>b</sup>	Decrease	Not affected	Decrease	Decrease	Decrease	—	Phosphatidic acid production decrease
Cirrhosis	Increase	Decrease	Both	Decrease	Decrease	Decrease	TNF- $\alpha$ , IL-6, IL-8 increase; FcR endocytosis decrease
SLE	Increase	Decrease	Increase	Decrease	Decrease	Decrease	CD11b increase, TGF- $\beta$ increase
Influenza virus	Increase	Decrease	Decrease	Decrease	Decrease	—	Apoptosis increase
HIV	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease	Apoptosis, CD11b, TGF- $\beta$ increase; ADCC decrease
Burn, trauma	Both	Decrease	Both	Decrease	Decrease	—	Monocyte HLA-DR decrease, CD11b increase

**NOTE.** ADCC, antibody-dependent cellular cytotoxicity; both, both increase and decrease reported; FcR, Fc receptor; HLA, human leukocyte antigen; NADPH, nicotinamide adenine dinucleotide phosphate; SLE, systemic lupus erythematosus; TGF, transforming growth factor.

<sup>a</sup> Some studies have shown increased function, and others have shown decreased function.

<sup>b</sup> Findings were mostly derived from studies of in vitro effects of ethanol on neutrophil responses.

duction and was associated with more-rapid healing of foot ulcers related to diabetes [11]. It should be noted that hyperglycemia may also depress the ability of phagocytes to kill certain organisms by direct effects on the organisms [12] or through inhibition of antimicrobial activity of collectins [13, 14].

## RENAL FAILURE

Bacterial infections are a major cause of morbidity and mortality among patients with end-stage renal disease [15–17]. Phagocyte function appears to be altered by uremia per se and by specific hemodialysis techniques. Phagocytic activities of neutrophils [18] and macrophages [17] are depressed in patients with advanced renal failure. Depression of macrophage phagocytosis in patients with renal failure was correlated with incidence of infection and improved by dialysis in a prospective study [17].

Proposed mechanisms for phagocyte dysfunction in uremia include elevated intracellular calcium concentrations in phagocytes [15, 19], iron overload [15, 20, 21], and “uremic toxins” that depress neutrophil function [15, 22, 23]. Calcium channel blockers, 1,25-dihydroxyvitamin D [19], and erythropoietin [15] have been reported to improve phagocyte function in patients with renal failure.

The use of cuprophane membranes in hemodialysis has been shown to cause significant alterations of neutrophil function. This type of membrane causes complement activation, release of LTB<sub>4</sub>, rapid up-regulation of CD11b/CD18 expression on the neutrophil cell surface, and transient neutropenia as a result of increased neutrophil adhesion and sequestration in the pulmonary vasculature [24, 25]. Although neutrophil counts recover, circulating neutrophils continue to overexpress adhesion receptors. Alternative hemodialysis membranes (e.g., polysul-

fone, cellulose acetate, polyacrylonitrile) do not have these effects. Patients who undergo dialysis with cuprophane membranes also have increased infectious morbidity and mortality compared with patients who undergo hemodialysis with alternative membranes [18, 25, 26]. It is possible that reduced use of cuprophane dialysis membranes and other improvements in care (e.g., routine use of erythropoietin and vitamin D) may account for the reported decrease in infectious mortality associated with renal disease [15].

## ALCOHOLISM AND HEPATIC CIRRHOSIS

Alcoholic persons are well known to be at risk for severe bacterial infections, especially bacterial pneumonia [27–31]. Incubation with ethanol in vitro reduces the ability of neutrophils to generate activating signals, produce superoxide, and kill bacteria [32–35], and it inhibits cytokine production by macrophages [36]. The inhibitory effects of ethanol on certain phagocyte functions may result from its ability to inhibit formation of phosphatidic acid in these cells [33]. Some of these effects of alcohol may be transient, because depressed neutrophil functions are observed in intoxicated alcoholic individuals [37], but not in healthy, well-nourished, persons with chronic alcoholism who are abstinent [38]. Leukopenia and an impaired myelopoietic responses to infection have also been described in persons with severe alcoholism [39, 40], although it is unclear whether these findings relate to prolonged alcohol exposure per se or other factors.

The spectrum of infections and the nature of phagocyte defects observed in cirrhotic patients differ somewhat from those associated with alcoholism per se (table 1) [41, 42]. Persons with cirrhosis appear to be particularly susceptible to pneumonia, bacterial peritonitis, urinary tract infections, and mor-

**Table 3. Difficulties in the evaluation of acquired phagocyte dysfunction.**

Problem	Description
Complexity of medical and surgical illnesses	<p>Evidence of (possibly aberrant) activation of phagocytes often coexists with evidence of phagocyte dysfunction and propensity to bacterial infection</p> <p>Depression of phagocyte activation may serve a physiologic function in protecting against organ injury (e.g., in sepsis, pregnancy, systemic lupus erythematosus)</p> <p>Phagocyte dysfunction may be only 1 of several factors impairing host defense; other concurrent factors often include injury to epithelial or mucosal barriers and impairments of B or T cell-mediated immunity</p> <p>Propensity to pyogenic or fungal infection for certain illnesses may be changing because of improvements in management of underlying condition (e.g., renal failure, HIV)</p> <p>Medical or surgical illnesses may have cooperative effects on phagocyte function (e.g., diabetes mellitus increases risk of bacterial infection during influenza virus infection or cardiac surgery)</p> <p>Relatively common genetic polymorphisms involving proteins involved in host defense (e.g., Fc receptors, myeloperoxidase, mannose-binding lectin) may contribute to risk of infection when combined with medical or surgical illnesses [116, 117]</p> <p>Bacterial infections per se may alter phagocyte function (e.g., <i>Streptococcus pyogenes</i> releases a C5a peptidase which impairs neutrophil chemotaxis [118] and <i>Clostridium perfringens</i> lyses neutrophils [119]); IL-10 elaborated during sepsis inhibits phagocyte function [120]</p>
Technical hurdles in assaying phagocyte function	<p>Lack of prospective validation of assays as predictors of infection</p> <p>Phagocytes can become activated during isolation procedure</p> <p>Assays are technically complex and not standardized between laboratories</p> <p>Phagocytes exuded into various tissue sites (e.g., soft-tissue, urinary or respiratory tracts) may have different functional attributes than those in blood</p> <p>The role of phagocyte response to, or production of, cytokines in vivo is only partially understood</p> <p>The physiologic roles of phagocyte-derived reactive oxygen and nitrogen species are not fully elucidated</p>

tality from bacteremia. Macrophage phagocytosis [43, 44] and some neutrophil functions [45] are impaired in patients with cirrhosis. Exaggerated proinflammatory cytokine responses in bacteremic patients with cirrhosis may contribute to mortality [46]. Murine studies indicate that bacterial trapping is important for resolution of bacteremia [47]. Further studies will be needed to determine whether vascular shunting in cirrhosis contributes to mortality due to bacteremia.

### AUTOIMMUNE DISEASES

Autoimmune diseases (e.g., systemic lupus erythematosus [SLE], rheumatoid arthritis) have been associated both with impaired neutrophil function and increased risk of infection. Among patients with SLE, bacterial infection is among the leading causes of morbidity and mortality [48–51]. Impaired macrophage phagocytosis has been documented in patients with SLE [52, 53]. Proposed mechanisms to account for impaired neutrophil function in autoimmune diseases include aberrant activation of circulating neutrophils as a consequence of complement activation (or other factors) [54] and inhibitory effects of antineutrophil antibodies [55]. In a murine model of SLE (i.e., MRL/lpr mice), elevated levels of transforming growth factor- $\beta$ , particularly in a form complexed with IgG, are as-

sociated with marked depression of neutrophil phagocytosis and increased mortality after challenge with *Staphylococcus aureus* [56]. Initial studies indicate that a similar mechanism may be responsible for impaired phagocytosis by neutrophils of patients with SLE [56].

### INFLUENZA VIRUS

Bacterial superinfections of the respiratory tract are a major cause of morbidity and mortality during influenza virus epidemics [57]. In vitro, influenza virus depresses phagocyte chemotaxis, degranulation, lysosome-phagosome fusion [58], respiratory burst responses [59], and bacterial killing [58]. Influenza virus also accelerates neutrophil and monocyte apoptosis, and markedly potentiates the apoptotic effects of *Escherichia coli* or *Streptococcus pneumoniae* in neutrophils [60–62]. Influenza-induced depression of neutrophil functions correlates with an increased susceptibility to bacterial superinfection in animal models [63, 64]. Depression of neutrophil function by influenza virus appears to be mediated largely by interactions of the viral hemagglutinin to sialylated neutrophil surface molecules [65, 66]. Other viruses that also bind to cells via a hemagglutinin appear to have similar effects [67–70]. The influenza virus nucleoprotein also inhibits neutrophil functions [71].

Although granulocyte-macrophage colony-stimulating factor (GM-CSF) has been shown to enhance respiratory burst responses of influenza virus-treated neutrophils [63, 72, 73], it did not improve host resistance to *S. pneumoniae* superinfection in influenza virus-infected chinchillas. Influenza virus-induced phagocyte dysfunction may be most pronounced in the airway itself. Vaccination has been shown to reduce the prevalence of bacterial pneumonia [74]. There are preliminary indications that inhibitors of influenza neuraminidase may also do this [75]. Collectins have been shown to inhibit infectivity and hemagglutination activity of influenza virus and to protect neutrophils from influenza virus-induced functional deficits in vitro [76]. Mice that lack pulmonary collectins have an increased severity of influenza, respiratory syncytial virus, and bacterial infection (A. M. LeVine et al., unpublished data) [77] that can be corrected by instillation of collectins.

## HIV

Phagocyte dysfunction may contribute to an increased frequency and severity of bacterial infections observed in patients with HIV [78–81]. Various neutrophil and monocyte functions, including chemotaxis [82–84], respiratory burst activity [85, 86], bacterial killing [87], and antibody-dependent cell-mediated cytotoxicity [88], are reduced in HIV-infected patients.

HIV infection is associated with accelerated neutrophil apoptosis [89] and autoantibodies directed against leukocyte integrins [90]. These abnormalities could contribute both to neutropenia and to neutrophil dysfunction [55, 91]. Elevated plasma levels of activated complement component C5 and IL-8 are observed in patients with HIV infection, along with depressed responses of neutrophils to these proteins [82], which suggests that neutrophils may be desensitized by prolonged exposure to these stimuli. HIV envelope proteins, like the influenza hemagglutinin, can cause phagocyte dysfunction by binding to functionally important phagocyte surface receptors. Binding of either the gp120 or gp41 components of the HIV envelope protein to monocyte chemokine receptors results in inhibition of chemotaxis and other responses to chemokines through receptor down-regulation [92]. There is some evidence that reduction of HIV load improves phagocyte function [93].

In one trial that compared treatment of patients with AIDS with IFN- $\gamma$  or IL-2, no bacterial infections were seen in subjects treated with IFN- $\gamma$ , whereas 17 of 52 IL-2-treated subjects had bacterial infections (including frequent bacteremia) [94]. However, this result may be more attributable to depression of neutrophil chemotaxis by IL-2 [95] than to beneficial effects of IFN- $\gamma$ . In a recent prospective, randomized trial, G-CSF treatment was shown to reduce the incidence and duration of bacterial infections in neutropenic subjects with advanced HIV infection [96].

## BURNS AND TRAUMA

Infections are a common cause of death in burn victims [97–99]. The types of infecting organisms [100, 101], and the fact that most serious infections involve sites other than the burn wound itself, both suggest that phagocyte dysfunction develops in patients with burns. There is evidence for both partial activation and depressed functional responsiveness in the circulating neutrophils of patients with burns. Impaired neutrophil adhesion, chemotaxis, and NADPH oxidase activity have also been documented in patients with burns [102–104]. Initial up-regulation of complement receptors (CR1 and CR3) on neutrophils has been noted after major burns and correlated with reduced neutrophil chemotaxis and decreased survival rate of burn victims [103]. These findings resemble those obtained with patients who underwent hemodialysis with cuprophane membranes. It is of interest that similar findings have been noted in severely traumatized patients as well [105–108]. Clinical trials of G-CSF, GM-CSF, or IFN- $\gamma$  in burn or trauma patients have been inconclusive [109–112]. In contrast, animal studies suggest that inhibition of phagocyte activation (e.g., through selectin blockade) may be beneficial in such patients [113].

During cardiopulmonary bypass, blood is exposed to non-physiologic surfaces, and there is evidence for release of proinflammatory cytokines and activation of complement and phagocytes that resemble those that are observed in hemodialysis with cuprophane membranes, burns, and trauma [114, 115]. In this instance, there is also evidence that blockade of activation (e.g., through inhibition of complement activation) may be beneficial.

## CONCLUSIONS

As outlined in this review, measurable abnormalities of neutrophil, monocyte, and macrophage function have been observed in a number of common medical and surgical conditions that are also characterized by an increased risk of bacterial and fungal infections (tables 1 and 2). Although the morbidity and mortality attributable to acquired phagocyte dysfunction appears to be vast, there are serious limitations of knowledge in this field. Few studies have tested prospectively whether abnormal measures of phagocyte function predict the likelihood of infectious complications, or whether interventions directed at improving or altering phagocyte function reduce such complications in medical and surgical conditions. Table 3 summarizes some of the obstacles that have hindered progress in understanding acquired phagocyte dysfunction.

An important barrier to the interpretation of observations in this field is that in vitro assays of phagocyte activation may be altered by nonspecific activation induced by cell isolation and preparation procedures. Furthermore, neutrophils isolated from the circulation may have distinct functional properties compared with those that have emigrated into tissue locations

[121–124]. Other aspects of neutrophil function in vivo that have received insufficient attention in studies of acquired phagocyte dysfunction include the role of cytokines in regulating neutrophil functions [56, 125, 126], the role of neutrophils as a source of cytokines [127, 128], and the role of phagocyte-derived oxidants as signaling molecules [129]. Clearly, the development of assays that more accurately reflect the in vivo functions of phagocytes remains a significant challenge.

Progress in understanding acquired phagocyte dysfunction will require prospective studies in which individuals at risk are assessed over time (e.g., see Zimmerli et al. [130]), as well as the development and validation of reproducible assays requiring minimal ex vivo manipulation of phagocytes [86]. Assays that directly reflect the activity of these cells at normal sites of function (e.g., measurements of neutrophil mobilization to sites of normal turnover, such as the oral mucosa [131]), should be particularly useful in this regard.

Despite these limitations, certain conclusions regarding acquired phagocyte dysfunction are possible. These functional abnormalities appear to occur via at least 3 distinguishable mechanisms. In patients with diabetes mellitus, uremia, and alcoholism, phagocyte dysfunction appears to be induced by the direct effects of metabolic disturbances (e.g., hyperglycemia) or chemical toxins (e.g., alcohol or its metabolites) on phagocytic cells. A second mechanism of acquired phagocyte dysfunction involves the effects of specific inhibitory molecules, such as viral proteins (see sections on influenza virus and HIV), specific autoantibodies [90], and cytokines (see section on SLE). On the other hand, phagocyte dysfunction associated with burns, extensive trauma, cardiopulmonary bypass, and hemodialysis appear to arise because of a pathologic activation of phagocytes in the systemic circulation (e.g., owing to systemic complement activation). Although much attention has been focused on phagocyte-mediated organ injury resulting from such activation, it is also likely that inappropriate activation of circulating phagocytes increases susceptibility to infection [132]. Pathologic activation of phagocytes in the systemic circulation appears to impair normal tissue distribution and to modify the activation potential of the cells.

There has been considerable interest in the use of recombinant cytokines (e.g., G-CSF, GM-CSF, IFN- $\gamma$ ) to enhance phagocyte function in clinical settings in which acquired abnormalities of phagocyte function have been described [11, 96, 133]. There is preliminary evidence that cytokine treatment may reverse acquired abnormalities of phagocyte function and enhance host defenses, particularly those clinical settings in which metabolic and chemical toxins or specific inhibitors have been implicated as mechanisms for these abnormalities. In these clinical settings, rigorous prospective studies, which examine reproducible measures of phagocyte function and the incidence of infection over time, would appear to be justified, particularly

in light of the continued emergence of antibiotic-resistant pathogens. In conditions characterized by aberrant activation of circulating phagocytes, other approaches (e.g., interventions that inhibit this activation) will be relevant.

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