Local application of human IgG to prevent biomaterial-centered bacterial infection
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Chapter 8

General discussion
“The antibiotic using community requested, and the drug makers spun out new, or modified versions of old antibiotics to treat the dozen major types of disease-causing bacteria. The consequence: bacteria were trained to find new ways to penetrate the defences.”

“Too few new drugs are being developed to replace those that have lost their effectiveness. In the race for supremacy, microbes are sprinting ahead.”
(World Health Report 1996, WHO)

Over the last two decades, the rapid evolution of antibiotic resistance has become a major problem in managing infectious diseases. With 80% of all Staphylococcus aureus isolates exhibiting resistance to methicillin in the United States\(^1\) and showing an increased resistance to vancomycin,\(^2\)-\(^6\) the era of antibiotics is unavoidably coming to an end.\(^7\),\(^8\) Fortunately, bacteria that acquire antibiotic resistance genetically do not change their surface characteristics or surface epitopes targeted by human IgG.\(^9\) Thus antibody opsonization remains effective in facilitating clearance by the host immune system. This thesis describes the investigation of an alternative method to prevent (biomaterial-centered) infection using locally applied, pooled polyclonal human IgG.

Results of the described research indicate that the behavior of Pseudomonas aeruginosa to a glass surface, resembling a biomaterial device, could be significantly influenced (Chapter 2) by the presence of IgG. Both the pre-adsorption of IgG to the glass surface, as well as the pre-opsonization of bacteria with IgG significantly reduced the initial deposition rates and increased the generation times of adherent bacteria. Visual observations of individual bacteria suggested that bacteria were physically inhibited from ‘stretching’ or cell body expansion prior to separation after their division in the presence of adsorbed immunoglobulins.

Subsequently, mouse-survival was significantly improved with prophylactic use of local IgG against lethal peritonitis challenges with the same bacterium as used on the glass surfaces (Chapter 3). The data indicated that locally delivered human IgG lowered the incidence and severity of infection by reducing locally the acute bacterial burden and cytokine production and systemically, by inhibiting sepsis.
However good results were achieved against different *Pseudomonads*, the efficacy of local human IgG to prevent biomaterial-centered infection in surgical wounds contaminated with methicillin-resistant *Staphylococcus aureus*, a clinically relevant organism in spinal implant infection (Chapter 4), was less convincing (Chapter 5). IgG-lavaged, stainless-steel K-wire implant sites showed significantly improved clinical signs of infection incidence and magnitude compared to saline-lavaged controls, corresponding with significant biofilm reduction on the implanted K-wires. Surrounding soft-tissues, however, still contained clinically significant numbers of viable bacteria in all the tested sites.

In the next stage, immune systems of mice potentiated by locally applied human IgG alone, could not overcome lethal bacterial challenges with *Escherichia coli* and *Klebsiella pneumoniae* (Chapter 6). Bacterial killing and therapeutic efficacies of a clinically routine prophylactic antibiotic (ceftazidime, 3\textsuperscript{rd} generation cephalosporin) was nonetheless significantly improved when administered \textit{in tandem} with locally applied IgG, leading to significantly improved survival results. In some cases, the combination therapy of local IgG and systemic antibiotics exhibited even synergistical benefits, that could be general to many other infections and could have important clinical implications for extending the clinical lifetime of front-line antibiotics facing resistance, as well as in treating antibiotic resistant infections.

In the end, (Chapter 7) the local, controlled delivery of human IgG from a gel-carrier directly to polypropylene implant sites prone to colonization and bacterial infection showed therapeutic potential and is advocated as a supplement to systemic antibiotic prophylaxis to potentiate the local host immune responses. Rapid release of bioactive antibodies in areas of bacterial contamination (e.g., appendicitis, open fractures) could function to clear pathogens via mechanisms that circumvent further antibiotic resistance, a role that complements the strengths and eliminates some of the weaknesses of current antibiotic prophylaxis, and one of our necessary future tools in the battle against (antibiotic-resistant) biomaterial-centered infection.
Future prospects

The blood-derived therapeutic IVIG is currently prepared in millions of doses annually, using Cohn fractionation and solvent/detergent treatment to eradicate possible bacterial and viral contamination. However, because of the concern of spreading blood-borne pathogens, IVIG products have been bypassed by various antibody technologies providing the means to generate unlimited amounts of monoclonal antibodies (Mabs) without any risk of viral- or prion-mediated disease transmission. Additionally, reduction in IVIG titers, resulting from careful blood donor screening and a general crisis in the short supply of IVIG worldwide, have both prompted new efforts to use Mabs to control antibody titers and supply. In recent years, major advances have been made beyond the original monoclonal hybridoma technology using mice\textsuperscript{10} to mass produce specific therapeutic Mabs, humanize murine Mabs\textsuperscript{11} and even generate human antibodies in plants.\textsuperscript{12-14} Currently, production costs for novel human or mouse Mab technology are significantly higher than the cost of pooled human IgG products. Nonetheless, the first monoclonal IgG products have entered clinical testing markets\textsuperscript{15-17} and can be effective in much lower doses than IVIG due to high specific antiviral or antibacterial titers.

For example, the human polyclonal hyperimmune anti-RSV globulin, Respigam\textsuperscript{®}, (MedImmune, Gaithersburg MD) exhibits at least a five-fold greater viral neutralization titer against RSV than standard IVIG.\textsuperscript{15} Recently, however, RespiGam\textsuperscript{®} was bypassed on the market by MedImmune’s monoclonal antibody product, Synagis\textsuperscript{™}, against RSV infection. This Mab demonstrates 50-100 times increased potency in the cotton rat model of RSV prophylaxis.\textsuperscript{16,17} Although seemingly expensive ($4,500 mean cost per five month anti-RSV-treatment session),\textsuperscript{18} the prophylaxis using RespiGam\textsuperscript{®} was still 15 times less expensive than one hospitalization for serious RSV infection, while RSV-related hospitalizations in prophylactically treated patients could be prevented by 41-57\%.\textsuperscript{19} Synagis\textsuperscript{™} is now the treatment of choice against RSV.

Global increase in Mab use will also allow companies to upscale Mab production, leading to a reduction in overall manufacturing cost and reduced wholesale prices of the final products. Production cost forecasts for “plantibodies”\textsuperscript{12-14} claim unit Mab costs of $10-100/g, bringing this raw material cost in line with other competitive drugs.
A major disadvantage of monoclonal antibody therapy, compared to the pooled polyclonal immunglobulins studied in this thesis, lies in the limited spectrum protection exhibited by Mab products due to the presence of highly specific antibacterial or antiviral antibodies targeting one epitope. Polyclonal antibodies exhibit broad specificities against families of epitopes or different epitopes on a single antigenic structure and, therefore, exhibit a wide range of binding activities and affinities against targets in different environments. Such a range results directly from various combinations of light and heavy chain primary sequences and their combinations (discussed in Chapter 1) to produce binding sites (Fab). However, biosynthetic design and productions of Mabs that specifically target antigenic epitopes common to entire strains or families of viruses or bacteria significantly reduces this disadvantage of monoclonal antibody prophylaxis or therapy. In the example of Synagis™, the antibody targets the so-called F protein that shows a high degree of cross-reactivity between subtypes of the RS-virus, rendering the therapeutic extremely effective against all current RSV strains. Likewise, antiherpes antibodies produced in plants are currently under development to prevent the spread of this sexually transmitted disease by local release of this therapeutic in the vagina.\textsuperscript{13}

Current prophylactic, generalized use of broad-spectrum antibiotics has a significant disadvantage over the application of pooled human IgG and future highly specific monoclonal antibodies in fighting infections. Antibiotics are not specifically directed against pathogenic microbes; Their microcidal action also eliminates commensal flora and viable cellular elements, essential components of the body’s armor against infection, therewith compromising the efficacy of the human immune response. These include strains of intraintestinal \textit{E. coli} responsible for digestion and other cellular immune elements. Reducing the antibiotic “overkill” will render immunotherapy-receiving patients more immunocompetent to prevent pathogenic colonization and infection by maintaining and exploiting their own flora.

Many companies are currently investigating the development of other anti-microbial Mabs, including anti-menigococcal, anti-pneumococcal, and anti-\textit{Borrelia Burgdorferi} (Lyme disease) antibodies (e.g., Smithkline-Beecham, Genentech, MedImmune,
Centacor, IDEC, NABI) with Mab designs selected carefully to target surface molecules conserved for centuries across species. Future Mab improvements and mixed Mab cocktail products will likely further broaden the current narrow spectrum of protection that characterize typical monoclonal antibodies.\textsuperscript{20,21} This will allow scientists to design and manufacture new anti-infective products that are badly needed to effectively address infectious disease in the antibiotic resistance era. However, current progress in new antibody and antibiotic synthesis may not be able to keep-up with the rapid increase in antibiotic resistant mechanisms and organisms. During this interim period where antibiotics are rendered less and less effective and potent monoclonal antibody therapies have not yet matured, hyperimmune pooled polyclonal immunoglobulins should prove very useful as a bridge therapy. By immediately opsonizing and paralyzing invading bacteria during surgical intervention within the “decisive period” resulting in possible infection,\textsuperscript{22,23} high titer, broad-spectrum IgG could assist the immune system to rapidly neutralize bacteria and significantly reduce biofilm formation and biomaterial-centered infection with pathogenic bacteria.

Subsequent combinations of systemic and local applications of monoclonal antibody cocktails, tailored towards specific bacterial and viral organisms and patient risk-groups, represent a logical evolution in this immunotherapy already identified in both scientific and laypersons literature. Experience gained using systemic and local applications of human IgG from many sources, by several application routes, and over many years will provide clinicians with the necessary knowledge, confidence and resources to develop non-blood derived monoclonal antimicrobials to effectively combat infections caused by antibiotic-resistant bacteria in this millenium.
References


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