

Review Article

Review on Antibody as A Drug of Choice

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Abstract

During the last 20 years, infectious diseases have indeed made a staggering comeback for a variety of reasons, including resistance against existing antibiotics. As a consequence, several alternatives to antibiotics are currently being considered or reconsidered. The modification of antibodies is of major interest since changes in their functionality and physico-chemical properties will broaden their application area. The features that make antibodies attractive drug candidates are high target specificity and their organization into distinct structural and functional domains. Antibody therapy has an increasing number of applications in which it is possible to use inexpensive sources of animal antibodies, such as bovine colostrum antibodies and egg yolk antibodies. A powerful way to fight infections in our days will be to use immune system as complement or replacement to antibiotics. The immune system and microorganisms have coexisted for millions of years and microorganisms have not become resistant towards them. But, its use is less than expected value still in developing countries including Ethiopia. Therefore, it is better if therapeutic and prophylactic antibodies are considered rather than antibiotics.

Keywords: Antibiotics, Antibody, Antigen, Immunity.

Introduction

The big load of antimicrobials (Antibiotics, Antimycotics and Antivirals) given both to man and animals is a threat to our environment with the menace to give a total imbalance between microbial species in humans, animals, plants, water and soil. Antibiotics are today found ubiquitous in our environment in constantly growing amounts and given to animals as "Growth Factors" especially to piglets, calves and chickens to avoid weaning diarrhea and to promote growth [1].

Antibiotics are distributed everywhere in animals and humans: blood, flesh, urine and feces. Antibiotic contaminated flesh is eaten both by humans and animals. Then, it excreted to the environment by urine and feces. Antibiotic factories spread out tons of antibiotics from their plants. Unused antibiotics are thrown away. Soil and water are enormous reservoirs for antibiotics. Soil-dwelling microbes encounter a myriad of antibiotics mostly in low concentrations. Low concentrations do not kill bacteria, but they will evolve strategies to resistance. Genetic spread of multidrug resistant bacteria is the biggest problem for propagation of antibiotic resistance [2]. However, the best defense for humans, mammals and birds against all kind of infectious agents has always been the immune system. A powerful way to fight infections in our days will

be to use this system as complement or replacement to antibiotics. Antibodies have a high specificity for binding and inactivating foreign substances including different microbes (Bacteria, Viruses, Fungi, and Protozoa). All mammals produce antibodies [3].

Antibodies are simply soluble forms of B-cell receptor secreted in to body fluids by activated B-cell that is used by immune system to identify and neutralize foreign objects such as bacteria and viruses; they all belong to the class of proteins called immunoglobulins. An antibody, also known as an immunoglobulin, is a large Y-shaped glycoprotein. Each of its tips contains a paratope that is specific for one particular epitope on an antigen, allowing these two structures to bind together with precision [4]. Using this binding mechanism, an antibody can tag a microbe or an infected cell for attack by other parts of the immune system, or can neutralize its target directly. The production of antibodies is the main function of the humeral immune system [5]. B cell receptor is only found on the surface of B cells and facilitates the activation of these cells and their subsequent differentiation into either antibody factories called plasma cells, or memory B cells that will survive in the body and remember the same antigen, so that the B cells can respond faster upon future exposure [6].

One of the main functions of fixation of complement is that lysis of cells and release of biologically active molecules. Another important function is binding to various cell types; phago-

cytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins newborn [4]. Now a days, scientists are using transgenic animals and plants to produce specific antibodies and are showing an innovative promise in future to solve many disease cost problems both in animal and human. However, the use and industrial production of monoclonal antibodies through the application of antibody engineering is still less than the expected value, mostly in developing countries including Ethiopia [7].

Therefore, the main objectives of this seminar paper are:

- To review and provide information on the therapeutic and prophylactic use of antibody
- To describe the maternal extension of antibodies
- To review and describe some application of antibody engineering.

An Overview on Antibody Therapies

General concept about Antibody

The typical Y-shaped structure of an antibody molecule consists of two identical heavy (H) and two identical light (L) chains, linked by disulfide bonds. All four chains consist of constant (C) and variable (V) domains. The lower part of the molecule, called the Fc region, is highly conserved between antibody classes, and mediates effector functions of antibodies. The upper arms of the antibody are referred to Fab regions. The V regions of both heavy and light chains combine to form two identical antigen binding sites. Within each V domain, amino acid sequence variation, and hence antigen recognition, is predominantly focused around three “hyper variable” regions. These residues are referred to as “Complementarity Determining Regions” (CDRs), (figure 1). CDRs from the variable heavy and variable light chain domains are juxtaposed to create the antigen binding site that recognizes the antigenic epitope, a specific location on the antigen [8, 9].

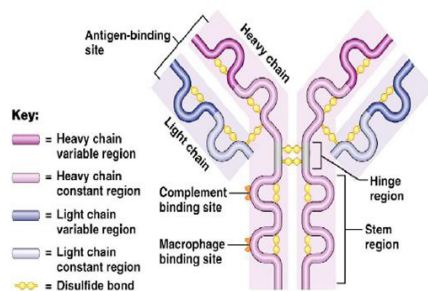


Figure: 1 Basic Antibody structure

Figure: 1 Basic Antibody structure

Source: [9]

An immunoglobulin monomer molecule consists of four polypeptide chains; two identical heavy chains and two identical

light chains connected by disulfide bonds. Each of these chains contains one variable domain and one constant domain [10]. Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen. Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM. The heavy chain constant domains corresponding to different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively [11].

Immunoglobulins function through binding specifically to one or a few closely related antigens. Each immunoglobulin actually binds to a specific antigenic determinant. Following binding to a specific antigen determinant, the immunoglobulins mediate a variety of effector functions that is required to overcome the antigen-antibody combination [9, 4].

Early Antibody Therapies

In the late nineteenth century, the German army doctor Emil von Behring (1854-1917), later the first Nobel Laureate for Medicine, pioneered the therapeutic application of antibodies. He used blood serum for the treatment of tetanus and diphtheria. When his data were mechanism to fight foreign toxic substances and that these substances should be present in the blood and therefore can be prepared from serum and used for therapy against toxins or infections. Antibody based (serum) therapies were first used to treat human infections in the 1890s [12,13]. In the early 20th century, serum therapy was used to treat a variety of bacterial infections, including those caused by *Corynebacterium diphtheria*, *Streptococcus pneumonia*, *Neisseria meningitides*, *Haemophilus influenza*, *group a streptococcus*, and *Clostridium tetani*. By the 1930s, serum therapy was standard treatment for lobar pneumonia. Several large controlled trials showed that administering type-specific serum reduced the death rate in patients with pneumococcal pneumonia by approximately 50 % [12].

In order to survive in a world laden with microorganisms, most multi-cellular organisms ought to depend on a network of host defense mechanisms which in most cases, involves several levels of interacting systems. Since the initial contact of fastidious microorganisms with the host usually occurs at inner or outer body surfaces, they should be the primary site for an immune reaction to occur. Thus, innate immune responses refer to the first line of host defense, which acts within a few hours after microbial exposure to mucosal surfaces. Upon recognition of conserved molecular microbial patterns such as PAMs or Pathogen-Associated Molecular Patterns (example, LPS and cell wall components) and Toll-Like Receptors (TLR) initiate the immune responses of the host [14-16].

Using the urinary and gastro-intestinal tract as model systems, information has been obtained on how organ and cell-specific expression patterns of TLR on epithelial cells correlate to the

ability of an organ to rapidly respond to bacterial infections has been obtained [17]. It has become clear now that understanding the innate response to pathogens will certainly provide insights to host defenses as well as the strategies used by pathogens to circumvent these defense mechanisms. Remarkably, the pattern-specific recognition system already acknowledged in animals, has also been reported in plants [18]. In complex system an invading microorganism can simply be eliminated by this primary reaction the innate response without requiring an activation of the adaptive immunity [19].

If the invading microbe outgrows the innate host defense, endogenous effector mechanisms of the innate system are up-regulated and have direct antimicrobial activity and mediator function to attract inflammatory cells and cells of the adaptive immune system. In lower eukaryotes, mostly invertebrates, the adaptive system is nonexistent, thus accounting for the versatile and effective role the innate system has in order to control, by itself, the invasiveness of a given pathogen [20].

Advantage of Antibody Based Therapy

Antibody molecules are assembled from combinations of variable gene elements, and the possibilities resulting from combining the many variable gene elements in the germ line enable the host to synthesize antibodies to an extraordinarily large number of antigens. During the generation of the antibody response, somatic mutations are introduced into immunoglobulin genes, which result in higher affinity antibodies and more diversity in specificity. Thus, antibodies are, as a class, broad-spectrum antimicrobial agents with activity against all classes of pathogens. However, individual antibodies are usually pathogen-specific and can control resistant micro-organisms and no disturbances in the normal host flora [21].

Antibodies are the best option for therapy and prophylaxis of a small number of viral diseases, for which antibiotics obviously are not a treatment option. Applications include pre-exposure prophylaxis of hepatitis B and varicella as well as treatment of viral diseases for which no vaccines or specific drugs are available, such as rabies and Ebola [22]. However, also bacterial diseases are on the list of candidates for antibody therapy, especially those for which preventive or therapeutic approaches are imperfect, not available, or no longer available. Pathogens include vancomycin-resistant *Enterococcus*, *Bordetella pertussis*, drug-resistant *Mycobacterium tuberculosis*, methicillin resistant *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [22, 23,24].

Antibody therapy has an increasing number of applications in which it is possible to use inexpensive Sources of animal antibodies, such as bovine colostrum antibodies and egg yolk antibodies. With the exception of the systemic administration of purified egg yolk antibodies against snake venoms [25-28], all these applications involve per oral administration of antibodies for the

treatment of enteric infections, such as enterotoxigenic *E. coli*, *Helicobacter pylori*, the dental caries causing *Streptococcus mutans*, and rotaviral infections [29].

Serum therapy is the administration of immune serum from immunized animals or convalescent humans for the prevention or treatment of infectious diseases, a sheep serum against diphtheria toxin [30]. Because, all that is required for efficacy of antibody treatment in the case of toxin-mediated infectious diseases is the formation of a stable immune complex between the toxin and the antibody, preventing the toxin from entering and damaging any target cells, it is not surprising that these were the first success stories of serum therapy. For instance, serum therapy reduced mortality from diphtheria from 50 to 80% to 6 to 15% [23].

Antisera against *cholera vibrios* could transfer immunity to control and kill the bacteria in vitro. Other examples include the immunoneutralization of tetanus toxin [31] and toxins responsible for scarlet fever (pyrogenic exotoxins) [23,32]. Although antibiotics kill microorganisms directly or interfere with their replication, antibodies use much more versatile mechanisms that include the promotion of phagocytosis at the site of infection, activation of the complement cascade followed by an inflammatory response and attraction of phagocytes, and initiation of antibody dependent cellular toxicity executed by monocytes, neutrophils, and Natural Killer (NK) cells. Its administration has the capacity to enhance immune function in immunosuppressed patients. In addition, antibodies can cause agglutination of bacteria and viruses, restrict mobility of the pathogen, and inhibit microbial metabolism and growth when binds to bacterial transporter proteins [24].

Although, the level of antibody immunity differs among pathogens, it may be possible to develop useful antibody therapies even if natural antibody immunity plays little or no role in protection. Two fungi, *Candida albicans* and *Cryptococcus neoformans*, are pathogens for which protective antibodies can be generated despite uncertainty about the role of natural antibody immunity [13]. The MAbs to *C. neoformans* enhance the therapeutic efficacy of amphotericin B [33,34], and 5-flucytosine. Therefore, uncertainty regarding the role of natural antibody immunity in protecting against a given pathogen does not rule out the existence of antibodies that may be useful in therapy [35].

Antibody-based therapies have low toxicities and high specificities. The high specificity of antibodies is both an advantage and a disadvantage. The advantage of high specificity is that antibody-based therapies target only the microorganism that causes disease and, it prevents development of resistance among non targeted microorganisms and avoids disturbance of the normal micro flora. In fact, in the case of serum therapy, numerous type-specific sera were developed for the treatment of pneumococcal pneumonia because only type-specific sera were effective against pneumococci [23,33].

As natural products of the immune system, antibodies can

interact with other immune components. Some mechanisms of antibody action, such as toxin and virus neutralization, complement activation, and direct antimicrobial functions, such as the generation of oxidants, are independent of other host immune components. In recent years, the recognition that antibodies can be immunomodulators, bridging the innate, acquired, cellular and humoral immune responses, has revealed new mechanisms of antibody-mediated immunity and has provided a better understanding of how and why antibodies are effective against microorganisms for which they do not mediate a direct biological effect [36].

The versatility of antibody technologies provides alternatives for countering antibody-resistant strains. For instance, new antibodies directed toward the mutated epitope could be developed, or antibodies that bind other antigenic targets could be introduced. Protease-producing strains could be countered with protease resistant immunoglobulin molecules generated by introducing amino acid changes at protease cleavage sites. In addition, the use of antibodies as therapeutic reagents has the advantage that there are several isotypes, which can function therapeutically in either an intact form or as fragments. In the intact molecule, the variable region (Fab) binds antigen, whereas the constant region (Fc) determines the biological properties of the immunoglobulin molecule, such as serum half-life, interaction with cellular Fc receptors and the ability to activate complement [37].

Historically, vaccine development for numerous infectious diseases was fuelled by antibody-based therapies and research into antibody mediated immunity. For example, successful passive antibody therapy against pneumococcal pneumonia and diphtheria preceded the development of vaccines against these diseases. More recently, the generation of protective MAbs against *Cryptococcus neoformans* and *Candidia albicans* identified polysaccharide antigens that were then used to design effective conjugate vaccines [38,39].

Protective antibodies to microbial polysaccharides can be used to identify Peptide mimotopes that elicit protective antibody responses [40], and antibodies that elicit protective anti-idiotypic responses can be used directly as immunogens. Efforts to develop antibody-based therapies can, therefore, promote vaccine development [41].

Limitation of Antibody Based Therapy

Even though excellent results were obtained with the neutralization of bacterial toxins, the variability and multiplicity of bacterial epitopes posed serious problems for the use of serum therapy against the majority of bacterial diseases. This is still true today; antibodies are a superior therapeutic choice for the neutralization of toxins (the use of Antisera against snake venoms), but treatment of other bacterial diseases requires fast and accurate microbiological diagnosis followed by swift and repeated administration of an adequate dose of high quality antiserum via a route

that will effectively reach the pathogen for neutralization. Indeed, there is unfortunately no such thing as an effective broad-spectrum antiserum. This requirement in most cases disqualifies antibodies as a first choice antimicrobial therapy [23,36].

Narrow specificity becomes a disadvantage in cases of mixed infections that cannot be treated with a single antibody preparation; therefore more than one antibody preparation might be required to target microorganisms with high antigenic variation. It also decreases the potential market for the drug. Moreover, genetic variability and immune evasion capabilities characterize many pathogens. Next to the challenge of antibody specificity, the production cost of sufficient quantities of high quality antibodies is considerable and certainly higher than the cost of routine chemotherapy [36].

Unless intended for therapy of enteric pathogens, therapeutic antibodies need to be administered systemically. In addition, systemic administration ideally requires antibodies of the same species in order to avoid anti-isotype immune reaction against the therapeutic agent, which is an obvious obstacle in human medicine [36]. The efficacy of therapeutic antibodies diminished rapidly after the onset of symptoms. The mechanism responsible for this is not well understood, but might reflect a rapid increase in the microbial burden in the animal, which are usually selected on the basis of their marked susceptibility to the agent [42].

A loss of efficacy with increased duration of infection or disease could limit the application of antibody based prophylaxis or conditions where an early diagnosis is possible. Recent advances in diagnostic microbiology, including polymerase chain reaction and nucleic acid hybridization, could substantially shorten the time required to establish a microbiologic diagnosis. The narrow spectrum of antimicrobial activity that characterizes antibody based therapies is a drawback for its commercial development [23].

Widespread use of antibody based therapies could produce selective pressure on microbial populations for the emergence of antibody-resistant variants. Antibody-resistant mutants of *Borrelia burgdorferi* have been produced in the laboratory [43], and may be selected in patients who undergo antibody based therapies. Microorganisms may become resistant to antibodies by acquiring mutations that change the antigenic site recognized by the antibodies or by producing proteases that destroy immunoglobulins [44].

Veterinary Use of Antibody as Maternal Extension

Antibody therapy and prophylaxis have a natural place in animal agriculture for the simple reason that mammalian species such as pigs, horses, sheep, and cows do not transmit maternal immunity prenatally (antibodies do not cross the barrier of the placenta, as is the case in humans) but postnatally through colostrum antibodies. In poultry, maternal antibodies are transmitted to the offspring via the yolk of the eggs [29,45-49]. As a consequence, colostrums and egg yolk were the first (and to the best of our knowledge still

the only) sources of antibodies that are routinely used for prophylaxis and therapy of infectious diseases in an agricultural setting, for which cost of antibody production, antibody production capacity, and simplicity of administration (i.e., orally, through the feed) are critical factors. Bovine colostrum and chicken egg yolks have indeed evolved naturally as antibody carriers per excellence, and colostrum was recognized as a vehicle for immune factors. During colostrum formation, immunoglobulins are transported across the secretory epithelium of the mammary gland by specific, receptor-mediated transport at a rate of as much as 500 g/wk. First colostrum contains between 30 and 200 mg of immunoglobulin per milliliter, the majority (75%) of which is IgG1 [46].

In a similar fashion, circulating antibodies in the plasma of a laying hen are transported by the granulosa cell layer and deposited into the yolk during the last days of oogenesis. An egg can contain as much as 25 mg of IgY per milliliter of yolk [50]. Antigen specific avian antibodies (IgY) have been used for numerous applications in medical and research fields. One of the most valuable and promising areas of its potential to be used for passive immunization to treat and prevent human and animal infections [51].

However, its clinical applications in humans are very scarce. But it is the functional equivalent to mammalian IgG and is the predominant immunoglobulin in egg yolk and also, actively transferred from the serum of the hen into the egg yolk to give immunity to embryos and chickens. This corresponds to placental IgG transfer in mammals to provide immunity to the fetus. The overall structure of avian IgY is similar to mammalian IgG, with two heavy and two light chains. A hen usually lays ~280 eggs in a year and an egg yolk contains 100-150 mg of IgY antibodies. This results in a yield of 28-42 g IgY per year per hen [52].

When a hen is vaccinated against a microbe, around 5%-10% of the IgY will react to this microbe. The production is simple, efficient and economical. It involves separation of the egg yolk from the white, followed by purification of antibodies from lipids and other materials. Therapeutic use can be produced from the egg yolk without any other ingredients than sterile water. It is stable at pH 4-9 and up to 65°C in aqueous condition. High salt conditions and stabilizing reagents (example, sucker) increases the stability to heat, acidic pH and high pressure. It can be easily administered orally for the treatment of gastrointestinal infections [53].

A fraction of immunoglobulins retain their neutralization activity in various segments of the gastrointestinal tract. A stronger activity would be easy to accomplish by buffers or in acid resistant capsules. This is the case only for the first 2 to 3 day of life; beyond this point uptake of intact antibodies no longer occurs, and any beneficial effects of antibody treatment need to be within the limits of the gastrointestinal environment. Those include challenges such as the acidic pH of the stomach and the presence of proteolytic en-

zymes; thus, natural transfer of maternal immunity is limited to the first couple of days of life. Without, human interference, per oral administration of antibodies beyond the time of enteric antibody absorption can indeed be quite effective [54].

Successful Application of Colostral and Egg Yolk Antibodies

The bulk of antibody treatment with colostrum and egg derived antibodies involves per oral treatment of enteric pathogens [47,55]. Applications are very similar in humans and in agricultural species; in principle, colostral antibodies and egg yolk antibodies seem to be used interchangeably. The best known examples include, the treatment of enterotoxigenic *E. coli* (ETEC) in humans [56], pigs [57], and calves [58], the dental caries causing bacteria *Streptococcus mutans* in humans [59,60], fatal salmonellosis in calves [61], and the treatment of gastric infections with *Helicobacter pylori* in humans [62,63]. Also enteric viral diseases are currently treated successfully with colostral or egg yolk antibodies. Those include rotaviral infections in humans [64,65], calves [66], and piglets [67] and corona viral infections in calves [68].

Limitations of Antibody Therapy in an Agricultural Context

Although the benefits of feed supplementation with pathogen-specific antibodies from hyper-immune colostrums and egg yolk are undisputed, it would be an exaggeration to call oral antibody therapy common practice, especially in an agricultural context. This undoubtedly has to do with the fact that production of standardized immune colostrum and egg yolk therapeutics, although theoretically and technically relatively simple, is labor intensive and, thus, cost intensive. As a consequence, these therapeutics are not used on a general scale (example, like antibiotics or vitamin and mineral supplements), and treatment of individual animals on a case by case basis represents an additional obstacle [29].

There is still a widespread misconception, that orally administered antibodies simply get digested and inactivated in the gastrointestinal tract, just like any other protein. Consequently, orally administered antibodies are not viewed as very effective drugs, at least not compared with small, simple, and stable molecules such as antibiotics. Although, it is true that orally administered antibodies are subjected to potential denaturation by the acidic pH of the stomach and degradation by proteases, active antibodies can still be detected in stool samples in percentages varying from very low levels to as much as 50% of the orally administered dose [29].

Studies have shown that parts of the antibodies remain intact in pepsin and trypsin digests, but there is considerable cleavage of the antibodies into Fab and F (ab')₂ fragments. It is important to note that these fragments still have the capability to bind to the antigen and display neutralizing activity. However, they may largely escape detection methods that depend on the presence of the anti-

body's Fc fragment that carries most of the isotypic determinants recognized by secondary reagents [69]. In addition, it is possible to administer antibodies in a stomach resistant formula in order to increase the ratio of intact antibodies in the intestine [70].

Application of Antibody Engineering in Veterinary Medicine

To avoid or reduce different kinds of losses due to animal disease cost, animal scientists are using biotechnology to develop an array of products to diagnose, treat (Table 1), and prevent disease in farm animals. Many animal diseases are difficult to diagnose. However, using biotechnology, scientists are developing fast, accurate diagnostic tests for many of the most common farm animal diseases and many of these new tests use monoclonal antibodies [71].

These antibodies are able to differentiate specifically those microbes that cause disease and that are vaccines. Example, veterinary clinicians and farmers use monoclonal antibodies to diagnose brucellosis in pregnant cattle, and then to prevent the spread of this infection by isolating carrier individuals from the rest of the herd. Monoclonal antibodies test also used for the diagnosis and treatment (by feeding it to calves or piglets that coat the offending bacteria then preventing the microbes from causing diarrhea) of scours in calves and piglets, to detect pregnancy [72].

Antibody Format	Application	Reference
scFv	Hepatocellular carcinoma therapy	[73]
dsFv	Cytotoxic recombinant anti-mesothelin immunotoxin	[74]
Anti CD22 recombinant immunotoxin	chemotherapy of resistant hairy cell leukemia	[75]
Fab	Anti-platelet iib/iiia inhibition of platelet aggregation	[76]
	Shiga toxin 1 neutralization	[77]

Table1: Various Antibody Format and Biotechnological or Therapeutic Application.

Source: Brichta [78].

Genetic engineering is also useful in generating large quantities of therapeutic proteins through inserting one or more new genes that are able to produce a natural disease fighting protein in to an animal (Figure 2). Interferon and interleukin-2 are natural proteins and are generated through genetic engineering to kill viruses and also to stimulate the animal's immune system, improving the immune system's ability to fight a disease. Antibody engineering technology is also used in the production of vaccines for swine pseudo rabies, a fatal herpes virus disease and for foot and mouth disease [79].

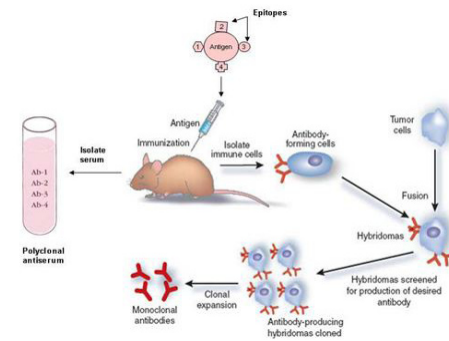


Figure 2: Overview of poly- and monoclonal antibody production.

Source: [80].

Since the introduction of hybridoma technology, it is becoming possible to accurately diagnose different protozoal and parasitic helminth infections of animals with the help of monoclonal antibodies that is specifically bind to specific epitope of the parasite antigen. Thus, monoclonal antibodies are able to accurately characterize and localize the parasitic antigen to the species level with the help of ELISA, PCR, radio immune assay and fluorescent immunoassay. Certain protozoal (Coccidiosis, Babesiosis, Theileriosis, Toxoplasmosis and Cryptosporidiosis) and helminth (Fasciolosis, Dirofilariosis, Trichinosis, and Cystic Echinococcosis) diseases of animals can be diagnosed accurately and treated with the help of monoclonal antibodies [81,82].

Monoclonal Antibodies

Monoclonal antibodies are antibodies that can recognizes a single and unique antigen surfaces specifically an epitope of an antigen and helps in the diagnosis of diseases caused by different pathogens [9]. The monoclonal antibodies being directed against single epitopes are homogeneous, highly specific and can be produced in unlimited quantities. Advances in genetic engineering over the years have provided numerous ways to design MAbs that are more robust and efficacious [83]. These are produced by fusing a cancerous cell with a cell that produces an antibody. Scientists create a hybridoma, which produces large quantities of identical or monoclonal antibodies in a pure, highly concentrated form. They produce these molecules by fusing two kinds of cells; one is an immune system cell that produces antibodies, which bind to part of a particular disease causing microbe; the other is a cancer cell [53,83,84,85].

Uses of Monoclonal Antibodies

Monoclonal antibodies or specific antibodies are now an essential tool of much biomedical research and are of great com-

mercial and medical value. Their uses are numerous and include prevention, diagnosis, and treatment of disease. They are especially useful in distinguishing morphologically similar lesions, like pleural and peritoneal mesothelioma, adenocarcinoma and in the determination of the organ or tissue origin of undifferentiated metastases, and also help in the detection of occult metastases by immuno-cytological analysis of bone marrow, other tissue aspirates, as well as lymph nodes and other tissues [86].

In animal disease diagnosis, they are very useful for identification and antigenic characterization of pathogens. They have also tremendous application in the field of diagnostics, therapeutics and targeted drug delivery systems, not only for infectious diseases caused by bacteria, viruses, and protozoa but also for cancer, metabolic and hormonal disorders [53]. Monoclonal antibodies can react with a single antigenic determinant and this restricted reactivity allows for precise identification of organism of interest which is the major advantage of MAbs over polyclonal Antisera. In case of a pathogen occurring as subtype defined by unique antigenic differences, specific MAbs can be used. Monoclonal antibodies are not used extensively in the animal world. They are employed in the process of genetically engineering an animal vaccine and are used mainly in the production of vaccines. Viruses, such as foot and mouth disease, are composed of large and complex proteins, all of which have many antibody binding sites [86].

Another use of monoclonal antibodies is a potential therapeutic role in preventing certain infectious diseases and some parasitic diseases. In this case, monoclonal antibodies that bind to hair like binding sites of the antigen of certain strains of intestinal bacteria, such as *Escherichia coli* (*E.coli*) are fed to new born calves or pigs. Then the bacteria will become to bind to the gut wall and then this will reduce the severity of the disease [9].

Polyclonal Antibodies

Polyclonal antibodies (Pabs) are produced by multiple B-cell clones, and as a population can recognize and bind with varying affinities to a variety of independent epitopes on a single antigen [60]. In a typical antiserum, only 5% of the Pabs are target-specific. Serum is a very good source of polyclonal antibodies. Further purification may be required, either to isolate the group of polyclonal antibodies or to isolate a specific antibody from the group [87,88].

The presence of several antibodies directed at different epitopes of the same antigen makes elution difficult and may damage the chromatography column and denature the antigen. Pabs are commonly obtained from sera of immunized animals, and are thus available in limited supply; it is often difficult to obtain multiple lots with consistent quality. To avoid these problems, it can be purified by affinity chromatography over a column of antigen to obtain antigen specific antibodies [89].

Conclusion and Recommendations

Normally, Antibodies are one of the most important B-cell Receptors that can be used as therapeutic and prophylactic treatment of infectious, non-infectious and parasitic disease those resistant to antibiotics and susceptible as well. Even though, the availability of many isotypes of immunoglobulins is not sufficient at everywhere and not used on general scale. Its therapy has an increasing number of applications in which it is possible to use inexpensive sources of animal antibodies, such as bovine colostrum antibodies and egg yolk antibodies. But its use is less than expected value still in developing countries including Ethiopia.

Based up on the above conclusion, the following recommendations are forwarded:

- Awareness creation about importance of antibodies to developing countries is very beneficial.
- It is superior, if isotypes of immunoglobulins is well available on market and used on general scale.
- It is better if therapeutic and prophylactic antibodies are considered rather than antibiotics.

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