Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
8 Control of intestinal diseases by dietary supplementation with antibodies

T. Stefaniak

Agricultural University in Wroclaw, Faculty of Veterinary Medicine, Department of Veterinary Prevention and Immunology, 31 C.K. Norwida Street, 50-375 Wroclaw, Poland

Due to the production conditions today about 20–40% of newborn farm animals (cattle, pigs, horses, goats, sheep) exhibit failure of passive transfer (FPT). The direct consequence of this is an increased susceptibility to diseases during the first weeks of life, which necessitates the wide use of antibiotics. As a further consequence, an increasing antibiotic-resistance of diarrheal strains of bacteria has become a fact. An alternative to using antibiotic is oral application of immunoglobulin products in the periods of greatest risk, i.e. within the first days of life and in the postweaning period. Air-dried egg yolk immunoglobulin (IgY), cow colostrum and swine serum, which can be produced on a large scale, provide the greatest chance for mass application. This work presents the most important principles of prophylactic and therapeutic, oral application of immunoglobulins on the basis of the published literature and the author’s own investigations.

1. INTRODUCTION

1.1. Immunity of the neonate’s gastrointestinal tract

The surface of the mucosal membranes exceeds by a hundred times that of the skin. It is at the mucosal membrane of the gastrointestinal tract that massive contact with the external environment occurs. Colonization of the host’s tissue by bacteria begins by the binding of bacterial surface adhesins with appropriate ligands on the host’s cells (Soto and Hultgren, 1999). Further stages involve breaking through the host’s defense, proliferation and damage of the host’s tissues (Kaper et al., 2004). Effective protection against potential infections via this route is a considerable challenge for the organism. The digestive tract protection system consists of natural barriers (epithelial continuity, mucus secretion, peristaltic motility, low pH of gastric juice, etc.); nonspecific humoral immunity factors (complement, lysozyme, defensins, etc.); nonspecific cellular immunity factors (macrophages, granulocytes, dendritic cells); specific humoral immunity (antibodies) and specific cellular immunity factors (T and B lymphocytes).
The efficiency of the immune system in the healthy animal depends on the cooperation of all the mechanisms mentioned above (Mueller et al., 1983; Sheldrake and Husband, 1985; Riedel-Caspari and Schmidt, 1991; Honorio-Franca et al., 1997).

Statistics concerning the occurrence of gastrointestinal tract pathology in young animals indicate that this age group is more often prone to the failure of organ protection systems. On the day of birth no specific immune cells are found in the neonate’s digestive tract. The colonization of the mucosal membrane lymphatic structures by lymphocytes takes place gradually. The first immune cells in the intestine are identified after 1–2 weeks of life (Navarro et al., 1997; Aminova et al., 2000) and their concentration comparable with that of adult animals is not achieved until after a few months of life. Until then the effectiveness of its self-active, specific, humoral and cellular immunity should be regarded as insufficient. The most important role is played by self-secretory IgA, the main mucosal immunoglobulin (Ig), of which a protective level is not achieved until after 2–4 weeks of life (Mestecky et al., 1991; Macpherson et al., 2001). However, the nonspecific immune mechanisms are efficient, although their activity may be slightly lower than that of adult animals (Mueller et al., 1983).

The observations mentioned above indicate that maintaining the gastrointestinal tract homeostasis in the first weeks of life depends to a large extent on the passive protection from maternal immunity (Stefaniak, 2000). Early drinking of colostrum provides supplemental antibodies for the gastrointestinal tract (Mellor and Murray, 1986). Due to the protection provided by maternal antibodies the microorganisms entering the neonate’s digestive tract (Korhonen et al., 1995; Palmeira et al., 2001) have limited success in attacking the mucosal membrane (fig. 1).

Other colostral components, such as immunomodulating and/or antimicrobial substances, including lactoferrin, lysozyme, lactoperoxidase and cytokines (Wagstrom et al., 2000; He et al., 2001; Blum and Baumrucker, 2002; Solomon, 2002) also have considerable significance for protection of the newborn. Furthermore, colostral components can also contribute to the cellular immunity, e.g. significant numbers of maternal cells may contribute to neonatal immunity, including phagocytes (neutrophils and macrophages), lymphocytes (B and T cells) and epithelial cells (Wagstrom et al., 2000). An interesting natural protective colostral mechanism is provided by the presence of soluble receptor analogs, which block the microbial adhesins and other pathogenic factors (Lindahl, 1989; Kelly and Younson, 2000). An example of this is the binding of F41 and K99 fimbrias of enterotoxigenic strains of Escherichia coli by glycoproteins present in cow and sow colostrum, and due to which pathogene adherence to intestinal epithelium of a neonate becomes weakened (Lindahl, 1989).

However, the most important protective role is played by specific antibodies against antigens present in the neonate’s environment (Riedel-Caspari, 1993; Korhonen et al., 2000b; Le Rousic et al., 2000; Crouch et al., 2001; Pisarska et al., 2002). Maternal antibodies, obtained from the colostrum and milk, protect the neonate against infections until its own efficient specific immune protection is developed (figs. 2 and 3).

A cow should produce at least 2 L of the first colostrum, containing at least 5% of Ig (50 g/L), which equals about 100 g per calf (Kruse, 1970; Tyler et al., 1999). In the study by Kruse (1970) 12% of cows did not give 2 L of colostrum and 30% showed an IgG concentration below 50 g/L. Similar data, obtained by Leveux and Ollier (1999), point to the fact that calves originating from primiparous cows are endangered by insufficient passive protection. Immunoglobulin concentrations in secretions of the ruminant mammary gland decrease rapidly after parturition and for instance in cow milk remain below 2 g/L at the 8th milking and below 1 g/L after the 15th milking (Leveux and Ollier, 1999). Insufficient quantity of
Control of intestinal diseases by dietary supplementation with antibodies

Protected gut mucosal membrane

Neutralization, immobilization, agglutination of pathogenic factors, clearance from the gut (with passage of dietary content)

Unprotected gut mucosal membrane

Inflammation, mucosal damage, hypersecretion, diarrhea

Fig. 1. Protection of the gut by specific antibodies. (a) Pathogenic factor attacking the unprotected mucosal membrane; (b) Protection due to early feeding with the immune colostrum, and/or prophylactic oral immunoglobulin supplementation. High concentration of antibodies protects the mucosal membrane. IgG = IgG antibodies (from colostrum or oral immunoglobulin supplementation); SIgA = SIgA antibodies (originating from colostrum or produced locally in low quantities within the gut of the young animal); s = specific receptor (to bacterial adhesins, toxins, viruses, etc.); ⚫ = pathogenic factor (bacterial, viral, toxic).
specific antibodies, or their inadequacy towards environmental microbes, facilitate early colonization of the neonate’s digestive tract as well as its susceptibility to diseases (fig. 4).

It is believed that the main role of the cellular components in mammary secretions is to interact with the development of local immunity in the newborn and to modulate active immunization of the neonatal intestine during this critical period, which is especially important to the development of the young (Le Jan, 1996; Barrington and Parish, 2001).

1.2. Failure of passive transfer (FPT) and its consequences to the neonate

In today’s production practices, about 20–40% of newborns of large farm animals (cattle, swine, horses, goats, sheep) develop failure of passive transfer (FPT) (Haława and Stefaniak, 2000). FPT means the acquired humoral specific immune deficiency of the neonate due to insufficient absorption of maternal, colostral immunoglobulins (fig. 5).

**Fig. 2.** Typical serum and secretory immunoglobulin levels and recommended period of oral immunoglobulin administration in healthy calves (M Ig – maternal Ig in calf serum; S Ig – self serum Ig; S Slg – self secretory Ig in the gut; Or Adm – recommended period of oral Ig administration; PL – assumed protective level).

Exhaustion caused by contact with antigen
Neonatal proteinuria
Protein catabolism
Secretion on to mucosal membranes

**Fig. 3.** Utilization of maternal immunoglobulins in neonates exemplified by a calf.
A direct consequence of this is an increased susceptibility to diseases in the first weeks of life. Calves exhibiting inadequate IgG concentrations are at greater risk of neonatal morbidity and preweaning mortality (McGuire et al., 1976; Vermunt, 1994; Wittum and Perino, 1995; Rea et al., 1996; Tyler et al., 1999), which necessitates the wide use of antibiotics. Because of the increasing antibiotic-resistance of bacterial strains, the common use of antibiotics, to protect the young animals against diarrhea, is becoming less and less effective. This is accompanied by raised consumer awareness of safe food (antibiotic-free) and the revised definition of safe food (Nikołajczuk and Molenda, 2000). Its new understanding points to food derived from animals kept in welfare conditions, without any antibiotic treatment throughout their life. This is another reason for withdrawing antibiotics and searching for alternatives (Kelly and Younson, 2000; Mine and Kovacs-Nolan, 2002).

Fig. 4. Gastrointestinal tract pathology as a result of insufficient colostral protection of a neonate (A = massive infection/ high pathogenicity, B = small quantity of the infectious agent/ moderate pathogenicity).

Fig. 5. Typical serum and secretory immunoglobulin levels and recommended period of oral Ig administration in calves with Failure of Passive Transfer (M Ig – maternal Ig in calf serum; S Ig – self serum Ig; Or Adm – recommended period of oral Ig administration; PL – assumed protective level; S SIg – self secretory Ig in the gut).
The binding of microbial adhesins to host receptor molecules is a critical early step in microbial infection and pathogenesis. Bacterial toxins also require at the first stage to bind with a specific ligand (Girardeau and Bertin, 1995). Exemplary well-recognized adhesins, bacterial enterotoxins and their appropriate ligands are presented in table 1.

Therefore, the possibility of blocking this interaction seems to be an attractive means of preventing infection at the early stage. Oral application of anti-adhesin antibodies is the most commonly used strategy of adhesion-blocking, but alternative aids are under investigation, especially adhesin analogues and receptor analogues (Kelly and Younson, 2000).

Orally administered specific antibodies against enteropathogenic viruses block the development of diarrhea resulting from infections with rota- and coronaviruses (Besser et al., 1988; Snodgrass et al., 1990; Heckert et al., 1999; Erhard et al., 1993; Ikemori et al., 1997).

There are two main periods of the highest risk of diarrhea (Frank and Kaneene, 1992; Vermunt, 1994; Sivula et al., 1996; Yokoyama et al., 1998), which require local immunity supplementation:
1. the neonatal period (age 0–14 days): the main risk factors are enterotoxigenic *E. coli* and rotavirus infection
2. postweaning period: associated with stress, changes in the feeding programme; the highest risk is during the first 2 weeks in the new environment.

Therefore, research into the wide application of immunoglobulins for the prophylaxis of animal gastrointestinal tract diseases ensues from ascertaining that the methods of health protection applied so far, based on massive antibiotic administration, have not been efficient enough and have caused numerous side effects. In contrast, the high efficiency of prophylactic and therapeutic oral application of antibodies is indicated in fig. 4.

2. DIETARY SUPPLEMENTATION WITH ANTIBODIES

One of the methods of treatment of acquired immune deficiency in young animals is oral application of immunoglobulin preparations containing antibodies directed against the incriminated digestive tract pathogens (Bogsted et al., 1996; Barrington et al., 2002). The most important sources of antibodies used in the protection of the alimentary tract of newborn farm animals are air-dried cow colostrum, egg yolk immunoglobulin and swine serum (Haines et al., 1990; Facon et al., 1993; LeRousic et al., 2000; Shibata et al., 2001; DeRouchey et al., 2003; Owusu-Asiedu et al., 2003a, b; Stefaniak et al., 2003). The choice of antibody source and its purification method need to be made in consideration of the circumstances of use, target animals, specificity, costs, quantity needed (table 2a and b).

2.1. The origin of orally applied antibodies

2.1.1. Allogenic (obtained from the same species, e.g. swine serum for piglets)

Allogenic antibodies cooperate with other host-specific immune mechanisms. Their main positive effect is the rapid elimination of pathogenic agents, but on the other hand, they can induce unintended tissue injury due to complement activation at the mucosal membrane (bystander effect). Bovine colostrum purified IgG was absorbed from calf neonatal intestine more effectively than native colostral immunoglobulins, air-dried colostral immunoglobulins or swine serum immunoglobulins given in similar concentrations (Arthington et al., 2000a, b). Absorbed allogenic immunoglobulins do not induce an immune response due to the intraspecies antigenic similarity. Passively acquired colostral IgG, anti-bovine rotavirus diffuse from blood to gut mucosal membranes up to the 10th day of calf life (Besser et al., 1988),
but in the case of intensive infections such antibodies are insufficient to protect the gastrointestinal tract against diarrhea. However, oral supplementation of calves with bovine colostral immunoglobulin concentrate resulted in higher serum immunoglobulin concentration within the first 4 weeks of life and additionally improved the weight gain and diminished the incidence of diarrhea (Nousiainen et al., 1994).

2.1.2. Xenogenic (obtained from different species, e.g. egg yolk immunoglobulin for mammals)

This kind of antibody could well merit common usage to protect the young animals. Important information about application of xenogenic antibodies is:

1. When administered during the period of Ig absorption from the gut to bloodstream (e.g. in foals before the 24th hour of life, in calves before 27–30th hour and in piglets, lambs and goat kids before 36–48th hour) xenogenic proteins appear in the blood of recipient animals – they stimulate the immune response against foreign epitopes present on the given immunoglobulins. In consequence, it leads to fast Ig elimination (removal of immune complexes) during 2–4 weeks after ingestion, although their absorption is not as effective as that of allogenic Ig (Stefaniak, 2002; Gąsowska and Stefaniak, 2003). In contrast, no absorption occurs and no such risks are observed in older animals (usually after 48 hours of life).

2. The lack of, or occurrence of less intensive interactions with the cooperating immune mechanisms, may be advantageous in the protection of a healthy gastrointestinal tract. Binding the specific antibodies to the pathogen (fig. 1) prevents interaction of the microbe with the mucosal membrane followed by immune exclusion (removal with the feces).

2.2. The most common antibody preparations administered orally

Practically, air-drying of egg yolk immunoglobulin, cow colostrum or swine serum is the only method, which allows large-scale production at low cost. Heat treatment reduces microbiological contamination of the final products, and allows their long-term storage. However, the most important disadvantage of air drying is the loss of antibody activity, which can reach over 50% (Stefaniak, 2002). The greatest denaturation and aggregation of cow immunoglobulins under the influence of temperature occur at pHs close to their isoelectric points (Lindström et al., 1994; Dominguez et al., 2001). The sensitivity of immunoglobulins to heat and their tendency to aggregation increase when there are low concentrations of salt in the solution. Although heat treatment (air-drying, pasteurization, UHT) causes a considerable decrease in the activity of specific antibodies (Korhonen et al., 2000a; Stefaniak, 2002), they still maintain restricted activity for months during their storage. Lyophilized antibodies preserve over 90% of their activity during 1 year storage (Stefaniak and Kopeć, 1997; Stefaniak, 2002, Stefaniak et al., 2004) and although they were also orally applied to young animals, relatively high costs and the low efficiency of freeze-drying has resulted in the abandonment of this method.

Egg yolk antibody from vaccinated laying hens seems to be a cheaper and good source of antibody (Jin et al., 1998). Simultaneous addition of spray-dried porcine plasma and egg yolk antibody to the fodder of early-weaned piglets appears to be an interesting idea (Owusu-Asiedu et al., 2003a).

The main immunoglobulin class in mentioned antibody sources is IgG. A comparison of the IgG of cattle, swine and hens is presented in table 3.
| Species/strain       | Adhesin /toxin         | Ligand on host enterocyte                            | References                  |
|---------------------|------------------------|------------------------------------------------------|-----------------------------|
| *Escherichia coli*  | fimbriae type 1 (MS)   | mannose                                              | Yuehuei and Friedman 2000   |
|                     | fimbriae type P (Pap)  | Gal-1,4-Gal                                          |                            |
|                     | fimbriae type G        | GlcNAc                                               |                            |
|                     | fimbriae type S        | sialic acid                                          |                            |
|                     | Intimin                | -translocated intimin receptor, Tir                  | Nougayrede et al. 2003      |
|                     | unknown receptors      | -other cellular receptors (β1-integrin?)             |                            |
| enteropathogenic    |                        |                                                      |                            |
| *Escherichia coli*  |                        |                                                      |                            |
| (EPEC)              | bundle-forming pilus   | unknown receptors                                     | Van den Broeck et al. 2000  |
|                     | and flagella           |                                                      |                            |
|                     | K88 or F4 fimbriae     | pig intestine                                        | Francis et al. 1999        |
|                     | K88ab (F4ab)           |                                                      | Yuehuei and Friedman 2000  |
|                     | K88ac (F4ac)           | IMTGP*, GP74**                                        |                            |
|                     | K88ad (F4ad)           | IMTGp                                                |                            |
|                     |                        | IGLad ***                                             |                            |
|                     |                        | bcd receptor - collection of glycoproteins with      |                            |
|                     |                        | molecular masses ranging from 45 to 70 kDa          |                            |
|                     |                        | bc receptor - two glycoproteins 210 and 240 kDa      |                            |
|                     |                        | b receptor - glycoprotein 74 kDa                      |                            |
|                     |                        | d receptor - glycosphingolipid with unknown          |                            |
|                     |                        | molecular mass                                        |                            |
|                     |                        | K99 (F5)                                              |                            |
|                     |                        | ganglioside containing neuraminic acid               |                            |
Shigella dysenteriae
enterohemorrhagic *E. coli*
(EHEC)
vero/shiga-toxigenic *E. coli* (VTEC/STEC)

| Organism | Toxin/Enterotoxin | Subunit | Receptor | Reference |
|----------|-------------------|---------|----------|-----------|
| Shigella dysenteriae | Vero/Shiga toxins (VT/Stx) A subunit (N-glycosidase activity against 28S rRNA) B subunit | Gb3 or Gb4 | membrane receptor | Gyles 1992 |
| Enterohemorrhagic E. coli (EHEC) | | | | |
| Vero/shiga-toxigenic E. coli (VTEC/STEC) | | | | |
| ETEC enterotoxin | LT enterotoxin subunit B STI (STa)- peptide of 18 or 19 amino acids. STII (STb) STa family | Glycolipids (GM1) or glycoproteins family of receptors unknown no data | Gyles 1992 Mainil 1999 |
| Escherichia coli | | | | |
| Vibrio cholerae non-O1 | NAG-ST | | | Nair and Takeda 1998 |
| Hakata strains of V. cholerae non-O1 | H-ST | | | |
| Vibrio mimicus | M-ST | | | Nair and Takeda 1998 (rev.) |
| Yersinia enterocolitica | Y-ST | | | Lucas and Corhier 1991 |
| Citrobacter freundii | C-ST | | | |
| Klebsiella pneumonia | STa-like enterotoxin | | | |
| Clostridium difficile | Toxin A (enterotoxin) | trisaccharide receptor | | Lyerly et al. 1988 |

* intestinal mucin-type sialoglycoprotein (IMTGP)
** intestinal transferrin (GP74)
*** intestinal neutral glycosphingolipid (IGLad)
| Animal species | Source of Ig | Specificity | Dosage | References |
|---------------|--------------|-------------|--------|------------|
| Cattle | IgY | *Cryptosporidium* sp. | 300 mg a day for 2 weeks (2 times a day 20 g of air-dried whole egg) | Erhard et al. 1997 |
| | | nonimmunized | 0.5–2 g/kg of body mass | Stefaniak 2002 |
| | | *E. coli* K99 and rotavirus | 8–16 g a day for first 10 days of life | Gąsowska and Stefaniak 2003, Erhard et al. 1995 |
| | | rotavirus/coronavirus/E. coli F5 | 2–10 g of air-dried whole egg twice a day for 10–14 days | Heckert et al. 1999 |
| | | *E. coli* K99/rotavirus | 11 g of air-dried whole egg twice a day for first 14 days of life | Erhard et al. 2000 |
| | | *Salmonella* | 1 g 3 times a day | Stefaniak et al. 2003 |
| | | bovine rotavirus/ *E. coli* K99/F41 | single additional feed 2 L within 12 h after birth | Yokoyama et al. 1998, Le Rousic et al. 2000 |
| | | Bovine serum | single feed 58–77 g IgG in 2.4–3.2 L | Todd et al. 1993 |
| | | nonimmunized | 10–25 g of air-dried plasma/L milk | Nollet et al. 1999 |
| | | Swine Cow col. | 2 weeks | Shibata et al. 2001 |
| | | IgY | 20% of basal liquid diet | Gomez et al. 1998 |
| | | nonimmunized | 0.5–2 g/kg of fodder, from 5th day up to weaning | Stefaniak et al. 2003 |
| | | ETEC (K88) | 64.5–100 mg in 5 ml solution | Yokoyama et al. 1993 |
| | | PED | 2–4 ml twice a day | Kweon et al. 2000 |
| | | Swine Whole egg IgY | 5% of milk replacer from 2 until 12 days of life | Hennig-Pauka et al. 2003 |
| | | ETEC (F4, F5, F6) | 3 g in 5 ml once a day for 3 days | Kellner et al. 1994 |
| | | ETEC (K88, K99, 987P)/ rotavirus | | |
| | | | | |
| | | | | |
| | | Goats | Cow col. | nonimmunized | Orsel et al. 2000 |
| | | | Horse | nonimmunized | Warko et al. 1993 |
| | | | Sheep | nonimmunized | Naciri et al. 1994, Klobasa et al. 1991 |
| | | | Frozen cow col. | *Cryptosporidium parvum* | Mellor and Murray 1986, Klobasa et al. 1994 |
| | | | Frozen ewe col. | | |
| Animal     | IgY or cow col. | Treatment | Amount and Duration | Reference                  |
|------------|----------------|-----------|---------------------|----------------------------|
| Mouse      |                | Mouse IgG from rabbit antiserum monoclonal antibody | **Vibrio cholerae O1 LPS** | Mukhopadhyay et al. 2000 Arrowood et al. 1989 |
| Mouse      |                | **Cryptosporidium parvum** | Antiserum | Arrowood et al. 1989 |
| Cattle     | IgY            | nonimmunized | 0.5–2 g/L of milk replacer, 2 weeks after weaning | Gąsowska et al. 2001 |
| Cattle     |                | IgY       | 2 g three times a day, for 2 weeks | Kuroki et al. 1997 |
| Cattle     |                | E. coli K99+ rotavirus | 2–10 g two times a day for 10–12 days | Heckert et al. 1999 |
| Cattle     |                | E. coli (K30, K99, F41) | 0.03–0.12 g three times a day for 7 days | Ikemori et al. 1992 |
| Cattle     |                | nonimmunized | 10–20% of spray-dried whole egg in milk replacer | Quigley 2002 |
| Cattle     |                | IgY or cow col. | twice a day for 7 days air-dried, high titer egg yolk or cow col. in 1–1.5 L of milk | Ikemori et al. 1997 |
| Cattle     |                | Milky | 0.5–2 g/kg of fodder, 2 weeks after weaning | Shibata et al. 2001 |
| Cattle     |                | nonimmunized | 2 g three times a day, for 2 weeks | Kuroki et al. 1997 |
| Cattle     |                | E. coli K99+ rotavirus | 2–10 g two times a day for 10–12 days | Heckert et al. 1999 |
| Cattle     |                | E. coli (K30, K99, F41) | 0.03–0.12 g three times a day for 7 days | Ikemori et al. 1992 |
| Cattle     |                | nonimmunized | 10–20% of spray-dried whole egg in milk replacer | Quigley 2002 |
| Cattle     |                | IgY or cow col. | twice a day for 7 days air-dried, high titer egg yolk or cow col. in 1–1.5 L of milk | Ikemori et al. 1997 |
| Cattle     |                | nonimmunized | 0.5–2 g/kg of fodder, 2 weeks after weaning | Gąsowska et al. 2001 |
| Cattle     |                | IgY       | 2 g three times a day, for 2 weeks | Kuroki et al. 1997 |
| Cattle     |                | E. coli K99+ rotavirus | 2–10 g two times a day for 10–12 days | Heckert et al. 1999 |
| Cattle     |                | E. coli (K30, K99, F41) | 0.03–0.12 g three times a day for 7 days | Ikemori et al. 1992 |
| Cattle     |                | nonimmunized | 10–20% of spray-dried whole egg in milk replacer | Quigley 2002 |
| Cattle     |                | IgY or cow col. | twice a day for 7 days air-dried, high titer egg yolk or cow col. in 1–1.5 L of milk | Ikemori et al. 1997 |
| Swine      | cow col.       | PED       | 0.5–2 g/kg of fodder, 2 weeks after weaning | Shibata et al. 2001 |
| Swine      | IgY            | nonimmunized | 0.5–2 g/kg of fodder, from 5th day up to weaning | Stefaniak 2002 |
| Swine      |                | nonimmunized | 0.5–2 g/kg of fodder, from 5th day up to weaning | Stefaniak et al. 2003 |
| Swine      |                | nonimmunized | 0.5–2 g/kg of fodder, from 5th day up to weaning | Stefaniak et al. 2003 |
| Swine      |                | ETEC (F18) | 1–5% of air-dried whole egg in fodder given 7–29 day postweaning | Zuniga et al. 1997 |
| Swine      |                | IgY and ADPP | 1.5 g of IgY in 5 ml orally 1–3 times a day for 3 days ad libitum fodder containing 5% of air-dried whole egg | Marquardt et al. 1999 |
| Swine      |                | ETEC (K88) | 0.2–0.3% of egg yolk powder, 5–10% of ADPP | Owusu-Asiedu et al. 2003a and 2003b |
| Swine      |                | nonimmunized | 5% of crude preparations to the fodder | Schmidt et al. 2003 |
| Swine      |                | nonimmunized | 5% of crude preparations to the fodder | Schmidt et al. 2003 |
| Swine      |                | nonimmunized | 5% of crude preparations to the fodder | Schmidt et al. 2003 |
| Mouse      | cow col.       | human rotavirus | 1% of body weight once a week, 6 times | Ebina et al. 1992 |
| Mouse      |                | E. coli O157:H7 | 1% of body weight once a week, 6 times | Funatogawa et al. 2002 |
| Geckos     | cow col.       | Cryptosporidium sp. | 1% of body weight once a week, 6 times | Graczyk et al. 1999 |
| Snakes     | cow col.       | Cryptosporidium sp. | 1% of body weight once a week, 6 times | Graczyk et al. 1998 |
| Guinea pig | cow col.       | Cryptosporidium parvum | 1% of body weight once a week, 6 times | Hoskins et al. 1991 |
| Chicken    | IgY            | nonimmunized | 1–2 g/kg of the fodder 2–42 day of life | Stefaniak et al. 2004 |
2.3. Cow colostrum

Cow colostrum is the only kind of colostrum used on a large scale, due to the large volume secreted and even some “overproduction” (Klobasa et al., 1991). Cow milk and colostrum are

Table 3
Characteristics of IgG from bovine colostrum, swine plasma and egg yolk

| Factor                                | Bovine IgG                              | Swine IgG                      | Egg yolk IgG (IgY) |
|---------------------------------------|-----------------------------------------|--------------------------------|-------------------|
| molecular weight                      | about 150 kDa between bovine and swine | about 170 kDa                  |                   |
| light chain                           | about 25 kDa                            | about 25 kDa                   |                   |
| heavy chain                           | about 50 kDa between bovine and swine   | about 68 kDa                   |                   |
| carbohydrate content                 | below 3% between bovine and swine       | up to 6%                       |                   |
| number of C\(_\text{H}\) domains      | 3                                       | 3                              | 4                 |
| PH-dependent destruction of secondary structure 70–72°C | at pH 2.0                              | at pH 2.0                      | at pH 2.0 sudden conformation changes below pH 4.0 |
| trypsin digestion susceptibility      | about 50% lost of antibody activity on the middle swine < bovine IgG\(_1\) < bovine IgG\(_2\) < chicken on the middle |   |                   |
| chymotrypsin digestion susceptibility | slight for IgG\(_1\)                    |                                 |                   |
| pepsin digestion susceptibility       | IgG\(_1\) more susceptible than IgG\(_2\) | (20 h) limited at pH 4.5 total at pH 3.5 |                   |
| protease inhibitors in the crude material molecular flexibility stepwise denaturation by guanidine-HCl protein A binding | colostral trypsin inhibitor serum protease inhibitors | ovoinhibitor ovomucoid |
|                                      | swine < bovine = chicken over 2.5 M solution over 2 M solution rapid denaturation over 2.5 M solution low affinity |                                      |
|                                      | high affinity, some differences between IgG\(_1\), IgG\(_{2a}\) and IgG\(_{2b}\) high affinity in 90% of serum IgG |                                      |
| approximate annual yield of IgG*     | 160–960 g/cow                           | 20–75 g/2 porkers              | 30–60 g/hen       |
| approximate annual IgG yield/ kg of body weight* aggregation in 1.5 M NaCl | 0.27–1.6 g                             | 0.09–0.34 g                   | 15–30 g           |
|                                      | slight                                  | slight                         | distinct          |

*assumption that the source of bovine immunoglobulin is colostrum, for swine – porker’s blood serum, for hens – the eggs of laying hens; the cow of 600 kg body weight supplies annually 4–8 L of first colostrum featuring Ig concentration 40–120 g/L; the porker gains its body weight of 110 kg within half a year – the blood collected at slaughter can supply 1–1.5 L blood serum/plasma of concentration 10–25 g Ig/L; the laying hen of 2 kg body weight lays about 300 eggs a year, containing 100–200 mg IgY.
(Data from: de Rham and Isliker, 1977; Brock et al., 1978; Bennell and Watson, 1980; Olsowska et al., 1982; McClead and Gregory, 1984; Shimizu et al., 1988; Linder et al., 1991; Shimizu et al., 1992; Hatta et al., 1993a,b; Shimizu et al., 1993b; Ternes et al., 1994; Quigley et al., 1995; Stefaniak, 2002.)
an attractive source of antibodies, willingly applied and easy to process. Bovine IgG1 prevails in colostrum and milk. When applied orally it is advantageously more resistant to digestion than other classes (de Rham and Isliker, 1977); resistance of this subclass to digestion is comparable to that of IgA. Bovine colostral secretory IgA would also resist proteolysis within the digestive tract, but the amount produced is very low (McClead and Gregory, 1984). The presence of trypsin inhibitor in colostrum provides for IgG1 protection; the inhibitor protects IgG1 from proteolytic degradation in the intestine and moreover its concentration is positively correlated to IgG1 concentration (Quigley et al., 1995). Orally given colostral antibodies derived from cows immunized with rotavirus or Clostridium difficile retain their activity after passage through human intestine (Roos et al., 1995; Kelly et al., 1997; Pacyna et al., 2001). Long-term in vitro digestion of colostrum whey with chymotrypsin resulted in maintenance of antibacterial IgG activity with simultaneous decline of IgM activity (Brock et al., 1978), while digestion with trypsin reduced IgG activity, but left IgM activity hardly changed. The authors determined the specific activity which required complete immunoglobulin molecules. In the digestive tract, the activity of the (Fab)2 fragment alone is quite sufficient to satisfactorily restrict the possibility of contact between the organism and the mucous membrane (Reilly et al., 1997). Protection of the mucosal membrane is maintained in spite of proteolysis of IgG and IgA immunoglobulin molecules (McClead and Gregory, 1984; Hilpert et al., 1987; Molla et al., 1988).

A well-known method of preventing diarrhea in neonatal calves is twice a day administration of surplus colostrum of the first and second milking mixed with milk or milk substitute throughout the period of the greatest risk of diarrhea, usually up to 10–12 days of life (Castrucci et al., 1984; Möstl and Bürki, 1988; Gutzwiller, 2002). Cow colostrum from nonimmunized cows or cows hyperimmunized with rotavirus, coronavirus, Escherichia coli or Shigella successfully prevents diarrhea also in neonates of other species (Brunser et al., 1992; Klobasa et al., 1994; Tzipori et al., 1994; Gomez et al., 1998; Ashraf et al., 2001; Shibata et al., 2001).

There are several indications for the application of cow colostrum to foals, lambs and kids (Klobasa et al., 1991; Winter and Clarkson, 1992; Perl et al., 1995):
- lack of, or low quality of maternal colostrum
- mastitis
- twins or multiple fetuses
- control of the infectious diseases transmitted through colostrum (caprine arthritis-encephalitis, maedi-visna, mycoplasmosis).

### 2.4. Yolk immunoglobulin (IgY)

IgY differs from mammal IgG in having a higher molecular weight, i.e. about 170 kDa, due to the occurrence of four C H domains in the heavy chain (Shimizu et al., 1988; Nakai et al., 1994). Egg yolk immunoglobulin displays high susceptibility to aggregation in salt solutions (1.5 M NaCl) and it is more susceptible to a decrease of pH to 2.0–4.0, as well as to digestion with proteolytic enzymes (trypsin, chymotrypsin) and is less heat-resistant than rabbit IgG (Shimizu et al., 1992; Hatta et al., 1993a, b). No considerable differences were found in the resistance to low pH, to proteolysis and to heat between IgY and cattle, goat and swine IgG (Shimizu et al., 1993b; Dominguez et al., 2001).

Egg yolk is a rich source of IgY, containing about 10–25 mg IgY/ml. From this value one can calculate that a single laying hen can produce 30–40 g IgY per year (Mine and Kovacs-Nolan, 2002). In proportion to animal body mass, the production volume of immunoglobulins
is several times higher than that from other comparable sources (such as rabbit and swine serum or cow colostrum). Noninvasive harvest of eggs, and easy IgY isolation are additional advantages (Tini et al., 2002). So far, IgY has been applied in prophylaxis and therapy in calves – against enterotoxigenic \textit{E. coli} K99, \textit{Salmonella} spp., rotaviruses, coronavirus, \textit{Cryptosporidium} spp.; in piglets – against enterotoxigenic \textit{E. coli} K99, K88 and 987P, and against rotaviruses; in mice – against rotaviruses; in rabbits – against enterotoxigenic \textit{E. coli}; also in humans – against enterotoxigenic and enteropathogenic \textit{E. coli}, rotavirus (Barz et al., 1980; O’Farrelly et al., 1992; Yokoyama et al., 1992; Erhard et al., 1996; Ikemori et al., 1997; Amaral et al., 2002). IgY preparations were successfully applied during the periods of the greatest risk, i.e. in neonates and in newly weaned animals. Yet, egg yolk immunoglobulin has not been used so far on a large scale in humans, except for Japan and South Korea, where it is an additive to yoghurts, sweets and baby food.

A single dose of 65 mg IgY, from hens immunized with \textit{E. coli} K88, assured specific antibody activity was present for up to 24 h in the colon of piglets aged 1–21 days (Yokoyama et al., 1993). When broiler chickens were given 0.5–1 g of IgY/kg feed, IgY antibody activity against \textit{E. coli} O157, \textit{Salmonella enteritidis}, \textit{S. typhimurium} and \textit{Klebsiella pneumoniae} were recorded in the feces. The intensity of the ELISA reaction was proportional to the IgY dose (Stefaniak et al., 2004).

Most studies involved the use of whole yolk from hens immunized with definite antigens on an experimental scale (Barz et al., 1980; Yokoyama et al., 1992; Rzedzicki and Wernicki, 1994; Erhard et al., 1996; Ikemori et al., 1997). Air-dried immunoglobulin preparations obtained from commercial eggs displayed antibody activity against diarrheal strains of \textit{Escherichia coli} O157, \textit{Salmonella enteritidis}, \textit{S. typhimurium} and \textit{Klebsiella pneumoniae} and was successfully applied (in the dose of 1–2 g/kg feed or 1 L of a milk-substituting preparation), in the prophylaxis of diarrhea in weaned calves as well as in suckling and weaned piglets (Stefaniak, 2002; Gąsowska and Stefaniak, 2003; Stefaniak et al., 2003). High levels of addition (5–20%) of spray-dried whole eggs can restrict the calves’ and piglets’ weight gain because of the presence of protease inhibitors in egg white, as well as because of the differences in amino acid content in egg as compared to the needs of those mammals (Quigley, 2002; DeRouchey et al., 2003; Owusu-Asiedu et al., 2003a, b).

2.5. Sera

Serum produced from the blood of slaughtered swine allows the large-scale production of immunoglobulins. A commonly used supplement of fodder is spray-dried porcine plasma – SDPP (DeRouchey et al., 2003; Schmidt et al., 2003). It contains the whole spectrum of serum proteins, including the biologically active ones. In the commonly proposed doses (5–10% addition to the fodder) it constitutes an important source of alimentary protein (Schmidt et al., 2003). In the proposed amounts it results in a considerable increase of feeding costs. Spray-dried swine plasma is commercially available in the USA and other countries and is applied orally to suckling and early-weaned piglets. Due to the savouriness of fodder containing SDPP the piglets eat it in higher amounts and achieve higher weight gains than the control piglets fed with standard fodder.

Rabbit immune serum was successfully applied orally to rats experimentally infected with a pathogenic \textit{E. coli} strain (Rivier and Sobotka, 1978). Immunoglobulins originating from cows immunized with \textit{V. cholerae} were introduced with satisfactory results concerning rabbit protection (Boesman-Finkelstein et al., 1989). Swine serum possesses IgG fractions with different resistance to cleavage by trypsin or pepsin (Ols ov ska et al., 1982). Because of the
fact that spray-dried blood serum preparations are significantly contaminated, it is advisable for them to undergo irradiation (DeRouchey et al., 2003).

2.6. Problems associated with oral application of immunoglobulins

An important problem with oral administration is proteolysis of the immunoglobulins by digestive enzymes, while another problem is caused by inactivation of antibody activity due to low pH. Irreversible inactivation of nonprotected IgY occurs at pH below 4. There are some methods proposed to protect the applied antibodies against proteolysis by gastric juice at low pH, e.g. use of hydroxypropyl methylcellulose phthalate (Ikemori et al., 1996). In the opinion of Ikemori and coworkers (1996) spray-drying of IgY with hydroxypropyl methylcellulose phthalate resulted in the protective binding or coating of antibodies. It enabled them to withstand acidic condition and to retain the antibody activity during the passage through the small intestine. Acid stability of IgY was enhanced in the presence of 30% sorbitol (Lee et al., 2002), or by encapsulation of IgY in the liposomes (Shimizu et al., 1993a).

Bovine IgG1 is the major immunoglobulin in cow colostrum and milk and it is more resistant to digestion than other immunoglobulin classes, which can be regarded as an advantage for oral administration (de Rham and Isliker, 1977). High doses of orally given immunoglobulins are more resistant to digestion and low pH within the gastrointestinal tract; at low concentrations their activity disappears before reaching the posterior segments of the intestine (Petschow and Talbott, 1994). On the other hand, IgG is susceptible to cleavage by bacterial proteases in the vicinity of hinge region, and indeed is more susceptible to cleavage than IgA, while IgA1 is more susceptible than IgA2 (Molla et al., 1988).

Orally given air-dried immunoglobulins of colostrum-supplements were only about one third as effectively absorbed by calves as immunoglobulins from fresh cow colostrum (Garry et al., 1996). Worse protection caused more frequent pathology in calves. Relatively low doses of air-dried IgY (0.5–2 g/kg body weight), supplied to newborn calves instead of or together with first colostrum, were absorbed from intestine to blood with only 4–8% efficacy (Stefaniak, 2002).

Cow colostrum given to lambs and goat kids during intestinal absorption of immunoglobulins may induce hemolytic anemia, caused by the binding of antibodies to recipient erythrocytes (Winter and Clarkson, 1992; Perl et al., 1995). Cow colostrum may also be the source of Mycobacterium paratuberculosis in goat kids (Orsel et al., 2000).

2.7. Hyperimmune versus normal antibodies

The products from hyperimmune animals are mostly (Ikemori et al., 1992; Kellner et al., 1994), but not always, more effective than those coming from nonimmune animals (Korhonen et al., 1995; Sarker et al., 2001). Loimaranta et al. (1998) showed that as little as 2–4 mg/ml of immune and nonimmune colostrum produced visible aggregates with Streptococcus mutans, which occurred in parallel to a reduction of bacterial adhesion. Lower concentrations, producing invisible aggregates, surprisingly increased bacterial adhesion. The authors believe that cow colostrum also contains other components causing Streptococcus aggregation.

Immunoglobulin preparations from nonimmune animals (e.g. air-dried swine serum pooled at slaughter) contain antibodies directed against a broad spectrum of antigens, which are produced during the animal’s life. When applied prophylactically, they may be effective in preventing the adhesion of infectious agents to the gut mucosal membrane and in protection against gastrointestinal tract pathology (Lissner et al., 1996; Stefaniak and Kopeč, 1997).
Highly specific immunoglobulin preparations derived from hyperimmunized animals show significantly higher efficiency regarding homologous antigens, but they may not have such broad activity against other pathogens as a pool of a large number of nonimmunized slaughter animals from many herds.

2.8. Factors affecting protective efficiency of orally administered antibodies

The choice of timing and duration of oral application of antibodies, their origin, specificity and method of application must be made on the basis of good knowledge about the farm in question (fig. 6). The management and quality of the environment have to be considered. The most important pathogenic factors for the digestive tract of the young animals should be exactly identified. The essential factor to be taken into account is economic assessment, because highly purified preparations from immunized animals may be too expensive for mass prophylactic application.

The Ig additive in feed or in a milk-replacer (table 4) seems to be the most suitable for prophylaxis, whereas application in capsules or the administration of Ig concentrate is advisable in diarrhea therapy (Kelly et al., 1997; Graczyk et al., 1998, 1999; Ashraf et al., 2001; He et al., 2001; Quigley et al., 2001; Solomon, 2002; Stefaniak et al., 2003, 2004).

As presented in fig. 6, a number of factors determine whether the oral application will fulfill the expected protective function; many of these factors do not depend on people or animals (Barrington et al., 2002; Stefaniak, 2002; Stefaniak et al., 2003). Awareness of these factors should contribute to proper diagnosis and to a reduction of the risk of diarrhea on a given farm (Frank and Kaneene, 1992).

3. FUTURE PERSPECTIVES

It seems that in the future, IgY preparations will become more and more important in the protection of the digestive tract of young mammals, since their production on a large scale is undoubtedly easier and less expensive than that of other antibodies (Schade and Hlinak, 1996).

The earlier investigation carried out by our team showed that there exists a wide cross-reactivity between the most frequent Gram-negative bacteria occurring in farm animals, while

---

**Fig. 6.** Factors affecting protective efficiency of orally administered antibodies (+ positive effect; – negative effect).
antibodies obtained from several animal species against *Haemophilus somnus* cross-react with antigens of *E. coli*, *Pasteurella multocida*, *P. haemolytica*, *Salmonella enteritidis*, *S. typhimurium*, *S. dublin* and *S. gallinarum-pullorum*, *Klebsiella pneumoniae* (Stefaniak et al., 1998, 1999; Wieliczko et al., 2000). Most of the cross-reacting antigens have a mass of 23–45 kDa (Stefaniak et al., 1998). Parenterally given *H. somnus* hyperimmune sera showed protective activity against infections caused by different Gram-negative bacteria (Nikołajczuk et al., 1996, Stefaniak et al., 1999).

It seems extremely attractive for field practice, to isolate the antigens responsible for induction of interspecies protection and the production of an effective subunit vaccine for immunization of laying hens, and then using egg donors as the source of IgY antibodies for the protection of young animals. Finding the least-invasive and low-cost immunization method, as well as achieving the high-titer-specific antibodies will become one of the most important tasks aimed at large-scale production (Hedlund and Hau, 2001). The decision concerning IgY doses for herds at high and low risk of infection will be a crucial step, which will contribute to the possibility of lowering the costs of protecting the young animals and obtaining the highest clinical effectiveness of the chosen preparation.

In the future, IgY is expected to be used in the prevention of epidemics of, e.g. typhus or cholera in environmental disasters, the treatment of diarrhea in risk-group patients – suffering from AIDS, in pregnant women and in the protection of the newborn with immune deficiencies or low birth weight (Kühlmann et al., 1988; Shimizu et al., 1988, 1994).

Further improvement in IgY purification is expected in the area of technological development concerning production of the preparation. It will have to take into account the relation between procedure costs and the protective effect of the preparation.

Strong expectations have been connected with experimental application of “plantibodies” – antibodies of required specificity and class, produced by transgenic plants (Ma et al., 1995; Larrick et al., 1998; Chadd and Chamow, 2001; Peeters et al., 2001). Transgenic plants may be suitable for diagnostic or therapeutic use, as well as for large-scale production of recombinant secretory immunoglobulin A for passive mucosal immunotherapy. The latter application may prove to be revolutionary in the field of efficient protection of young animals.
against infections, because of its low costs and the large scale of immunoglobulin production (Hiatt and Ma, 1993; Sharp and Doran, 2001). Theoretically, obtaining immunoglobulins from transgenic plants considerably exceeds the amounts which can be produced from animals.

REFERENCES

Amaral, J.A., Tino De Franco, M., Carneiro-Sampaio, M.M.S., Carbonare, S.B., 2002. Anti-enteropathogenic Escherichia coli immunoglobulin Y isolated from eggs laid by immunised Leghorn chickens. Res. Vet. Sci. 72, 229–234.

Aminova, G.G., Grigorijenko, D.E., Rusina, A.K., Jerofiejeva, L.M., 2000. Morphological characteristics of the lymphoid tissues in the newborn children. In Russian. Morfologiia 118, 53–56.

Arrowood, M.J., Mead, J.R., Mahrt, J.L., Sterling, C.R., 1989. Effects of immune colostrum and oral administered antisporozoite monoclonal antibodies on the outcome of Cryptosporidium parvum infections in neonatal mice. Infect. Immun. 57, 2283–2288.

Arthington, J.D., Cattell, M.B., Quigley, J.D., 2000a. Effect of dietary IgG source (colostrum, serum, or milk-derived supplement) on the efficiency of Ig absorption in newborn Holstein calves. J. Dairy Sci. 83, 1463–1467.

Arthington, J.D., Cattell, M.B., Quigley, J.D., McCoy, G.C., Hurley, W.L., 2000b. Passive immunoglobulin transfer in newborn calves fed colostrum or spray-dried serum protein alone or as a supplement to colostrum of varying quality. J. Dairy Sci. 83, 2834–2838.

Ashraf, H., Mahalanabis, D., Mitr, A.K., Tzipori, S., Fuchs, G.J., 2001. Hyperimmune bovine colostrum in the treatment of shigellosis in children: a double-blind, randomized, controlled trial. Acta Paediatr. 90, 1373–1378.

Barrington, G.M., Parish, S.M., 2001. Bovine neonatal immunology. Vet. Clin. N. Am. Food Anim. Pract. 17, 463–476.

Barrington, G.M., Gay, J.M., Evermann, J.F., 2002. Biosecurity for neonatal gastrointestinal diseases. Vet. Clin. N. Am. Food Anim. Pract. 18, 7–34.

Barz, C.R., Conklin, R.H., Tunstall, C.B., Steele, J.H., 1980. Prevention of murine rotavirus infection with chicken egg yolk immunoglobulins. J. Infect. Dis. 142, 439–441.

Bennell, M.A., Watson, D.L., 1980. The interactions of porcine and ovine, serum and colostral immunoglobulins with staphylococcal protein A. Microbiol. Immunol. 24, 871–878.

Besser, T.E., Gay, C.C., McGuire, T.C., Evermann, J.F., 1988. Passive immunity to bovine rotavirus infection associated with transfer of serum antibody into the intestinal lumen. J. Virol. 62, 2238–2242.

Blum, J.W., Baumrucker, C.R., 2002. Colostral and milk insulin-like growth factors and related substances: Mammary gland and neonatal (intestinal and systemic) targets. Domest. Anim. Endocrinol. 23, 101–110.

Boesman-Finkelstein, M., Walton, N.E., Finkelstein, R.A., 1989. Bovine lactogenic immunity against cholera toxin-related enterotoxins and Vibrio cholerae outer membranes. Infect. Immun. 57, 1227–1234.

Bogstedt, A.K., Johansen, K., Hatta, H., Kim, M., Casswall, T., Svensson, L., Hammarström, L., 1996. Passive immunity against diarrhoea. Acta Paediatr. 85, 125–128.

Brock, J.H., Pineiro, A., Lampreave, F., 1978. The effect of trypsin and chymotrypsin on the antibacterial activity of complement, antibodies, and lactoferrin in bovine colostrum. Ann. Rech. Vet. 9, 287–294.

Bruner, O., Espinoza, J., Figueroa, G., Araya, M., Spencer, E., Hilpert, H., Link-Amster, H., Brüsw, H., 1992. Field trial of an infant formula containing anti-rotavirus and anti-Escherichia coli milk antibodies from hyperimmunized cows. J. Pediatr. Gastroenterol. Nutr. 15, 63–72.

Castrucci, G., Frigeri, F., Ferrari, M., Cilli, V., Caleffi, F., Aldrovandi, V., Nigrelli, A., 1984. The efficacy of colostrum from cows vaccinated with rotavirus in protecting calves to experimentally induced rotavirus infection. Comp. Immunol. Microbiol. Infect. Dis. 7, 11–18.

Chadd, H.E., Chamow, S.M., 2001. Therapeutic antibody expression technology. Curr. Opin. Biotechnol. 12, 188–194.

Crouch, C.F., Oliver, S., Francis, M.J., 2001. Serological, colostral and milk responses of cows vaccinated with single dose of a combined vaccine against rotavirus, coronavirus and Escherichia coli F5 (K99). Vet. Rec. 149, 105–108.

De Rham, O., Isliger, H., 1977. Proteolysis of bovine immunoglobulins. Int. Arch. Allergy Appl. Immunol. 55, 61–69.
DeRouchey, J.M., Tokach, M.D., Nelssen, J.L., Goodband, R.D., Dritz, S.S., Woodworth, J.C., James, B.W., Real, D.E., 2003. Effect of irradiation of individual feed ingredients and the complete diet on nursery pig performance. J. Anim. Sci. 81, 1799–1805.

Dominguez, E., Perez, M.D., Puyol, P., Sanchez, L., Calvo, M., 2001. Effect of pH on antigen-binding activity of IgY from bovine colostrum upon heating. J. Dairy Res. 68, 511–518.

Ebina, T., Ohta, M., Kanamaru, Y., Yamamoto-Osumi, Y., Baba, K., 1992. Passive immunizations of suckling mice and infants with bovine colostrum containing antibodies to human rotavirus. J. Med. Virol. 38, 117–123.

Erhard, M.H., Kellner, J., Eichelberger, J., Lösch, U., 1993. Neue Möglichkeiten in der oralen Immunprophylaxe der Neugeboreendiarrhoe des Kalbes – ein Feldversuch mit spezifischen Eiantikörper. Berl. Münch. Tierärztl. Wochenschr. 106, 383–387.

Erhard, M.H., Lösch, U., Stangassinger, M., 1995. Intestinal absorption of homologous and heterologous immunoglobulin G in newborn calves. Z. Ernährungswiss. 34, 160–163.

Erhard, M.H., Bergmann, J., Remner, M., Hofmann, A., Heinritz, K., 1996. Prophylaktische Wirkung von spezifischen Dotterantikörper bei Escherichia coli K88 (F4) – bedingten Durchfallerkrankungen von Absatzziertieren. J. Vet. Med. A. 43, 217–223.

Erhard, M.H., Göbel, E., Lewan, B., Lösch, U., Stangassinger, M., 1997. Zur systemischen Verfügbarkeit von bovinem Immunglobulin G und Hüner-Immunglobulin Y aus gefüttertem Kolostrum bzw. Volleipulver bei neugeborenen Kälbern. Arch. Anim. Nutr. 50, 369–380.

Erhard, M.H., Leuzinger, K., Stangassinger, M., 2000. Untersuchungen zur prophylaktischen Wirkung der Verfütterung eines Probikuitums und von erregerspezifischen Kolostrum- und Dotterantikörpern bei neugeborenen Kälbern. J. Anim. Physiol. Anim. Nutr. 84, 85–94.

Facon, M., Skura, B.J., Nakai, S., 1993. Potential for immunological supplementation of foods. Food Agric. Immunol. 5, 85–91.

Francis, D.H., Erickson, A.K., Grange, P.A., 1999. K88 adhesins of enterotoxigenic Escherichia coli and their porcine enterocyte receptors. Adv. Exp. Med. Biol. 473, 147–154.

Garry, F.B., Adams, R., Cattell, M.B., Dinsmore, R.P., 1996. Comparison of passive immunoglobulin transfer to dairy calves fed colostrum or commercially available colostral-supplement products. JAVMA 208, 107–110.

Gazesowska, A., Stefaniak, T., 2003. Ocena efektów doustnego podania immunoglobuliny żółtka jaja (IgY) ciełcem w okresie wchłaniania makromolekuł z jelita. Folia Univ. Agric. Stetin. Zootech. 233(45), 87–92.

Gazesowska A., Stefaniak T., Kopec W., 2001. Wstępne wyniki zastosowania immunoglobuliny żółtka jaja dla ochrony cieł aç przenoszonych do ciełacisk. Folia Univ. Agric. Stetin. Zootech. 225(43), 45–48.

Girardeau, J.-P., Bertin, Y., 1995. Plins of fimbrial adhesins of different member species of Enterobacteriaceae are structurally similar to the C-terminal half of adhesin proteins. FEBS Lett. 357, 103–108.

Gomez, G.G., Phillips, O., Goforth, R.A., 1998. Effect of immunoglobulin source on survival, growth, and hematological and immunological variables in pigs. J. Anim. Sci. 76, 1–7.

Grazcyk, T.K., Cranfield, M.R., Helmer, P., Fayer, R., Bostwick, E.F., 1998. Therapeutic efficacy of hyperimmune bovine colostrum treatment against clinical and subclinical Cryptosporidium serpentis infections in captive snakes. Vet. Parasitol. 74, 123–132.

Grazcyk, T.K., Cranfield, M.R., Bostwick, E.F., 1999. Hyperimmune bovine colostrum treatment of moribund Leopard geckos (Eublepharis macularius) infected with Cryptosporidium sp. Vet. Res. 30, 377–382.

Gutzwiller, A., 2002. Effect of colostrum intake on diarrhoea incidence in new-born calves. Schweiz. Arch. Tierheilkd. 144, 59–64.

Gyles, C.L., 1992. Escherichia coli cytotoxins and enterotoxins. Can. J. Microbiol. 38, 734–746.

Haines, D.M., Chelack, B.J., Naylor, J.M., 1990. Immunoglobulin concentrations in commercially available colostrum-supplement products. JAVMA 208, 107–110.

Halawa, W., Stefaniak, T., 2000. Indeks immunoglobulín całkowitych u ciełac w Przedsiebiorstwie Rolnym “DS”. In: Ślebodziński, A.B. (Ed.), Noworodek a Srodowisko. Poznań, pp. 45–49.
Hatta, H., Tsuda, K., Akachi, S., Kim, M., Yamamoto, T., 1993a. Productivity and some properties of egg yolk antibody (IgY) against human rotavirus compared with rabbit IgG. Biosci. Biotechnol. Biochem. 57, 450–454.

Hatta, H., Tsuda, K., Akachi, S., Kim, M., Yamamoto, T., Ebina, T., 1993b. Oral passive immunization effect of anti-human rotavirus IgY and its behavior against proteolytic enzymes. Biosci. Biotechnol. Biochem. 57, 1077–1081.

He, F., Tuomola, E., Arvilommi, H., Salminen, S., 2001. Modulation of human immune response through orally administered bovine colostrum. FEMS Immunol. Med. Microbiol. 31, 93–96.

Heckert, H.P., Bardella, I., Hofmann, W., Oltmer, S., 1999. Untersuchung zum Einfluss eines antikörperhaltigen Voleipulvers auf die aktive Immunitätsbildung bei Kälbern. Dtsch. Tierärztl. Wochenschr. 106, 10–14.

Hennig-Pauka, I., Stelljes, I., Walldmam, K.H., 2003. Studies on the effect of specific egg antibodies against Escherichia coli infections in piglets. Dtsch. Tierärztl. Wochenschr. 110, 49–54.

Hedlund, G.P., Hau, J., 2001. Oral immunisation of chickens using cholera toxin B subunit and Softigen as adjuvants results in high antibody titre in the egg yolk. In Vivo 15, 381–384.

Hiatt, A., Ma, J.K., 1993. Characterization and applications of antibodies produced in plants. Int. Rev. Immunol. 10, 139–152.

Hilpert, H., Brüssow, H., Mietens, C., Sidoti, J., Lerner, L., Werchau, H., 1987. Use of bovine milk concentrate containing antibody to rotavirus to treat rotavirus gastroenteritis in infants. J. Infect. Dis. 156, 158–166.

Honorio-Franca, A.C., Carvalho, M.P.S.M., Isaac, L., Trabulsli, L.R., Carneiro-Sampaio, M.M.S., 1997. Colostral mononuclear phagocytes are able to kill enteropathogenic Escherichia coli opsonized with Colostral IgA. Scand. J. Immunol. 46. 59–66.

Hoskins, D., Chrisp, C.E., Suckow, M.A., Fayer, R., 1991. Effect of hyperimmune bovine colostrum raised against Cryptosporidium parvum on infection of guinea pigs by Cryptosporidium wrairi. J. Protozool. 38, 185S–186S.

Ikemori, Y., Kuroki, M., Peralta, R.C., Yokoyama, H., Kodama, Y., 1992. Protection of neonatal calves against fatal enteric colibacillosis by administration of egg yolk powder from hens immunized with K99-piliated enterotoxigenic Escherichia coli. Am. J. Vet. Res. 53, 2005–2008.

Ikemori, Y., Ohta, M., Umeda, K., Peralta, R.C., Kuroki, M., Yokoyama, H., Kodama, Y., 1996. Passage of chicken egg antibody treated with hydroxypropyl methylcellulose phthalate in the gastrointestinal tract of calves. J. Vet. Med. Sci. 58, 365–367.

Ikemori, Y., Ohta, M., Umeda, K., Icatlo, F.C., Jr., Kuroki, M., Yokoyama, H., Kodama, Y., 1997. Passive protection of neonatal calves against bovine coronavirus-induced diarrhea by administration of egg yolk or colostrum antibody powder. Vet. Microbiol. 58, 105–111.

Jin, L.Z., Baidoo, S.K., Marquardt, R.R., Frolich, A.A., 1998. In vitro inhibition of adhesion of enterotoxigenic Escherichia coli K88 to piglet intestinal mucus by egg-yolk antibodies. FEMS Immunol. Med. Microbiol. 21, 313–321.

Kaper, J.B., Nataro, J.P., Mobley, H.L.T., 2004. Pathogenic Escherichia coli. Nat. Rev. Microbiol. 2, 123–140.

Kelly, C.P., Chetham, S., Keates, S., Bostwick, E.F., Roush, A.M., Castagliulo, I., LaMont, J.T., Pothoulakis, C., 1997. Survival of anti-Clostridium difficile bovine immunoglobulin concentrate in the human gastrointestinal tract. Antimicrob. Agents Chemother. 41, 236–241.

Klobasa, F., Heribert, B., Kallweit, E., 1991. Substitution von Schafkolostrum durch Rinderkolostrum bei neugeborenen Lämmer. Züchtungskunde 63, 113–123.

Klobasa, F., Greimann, H., Kallweit, E., 1994. Untersuchungen zum quantitativen Übergang von Immunoglobulinen aus dem Darm in die Blutbahn neugeborener Lämmer. Berl. Münch. Tierärztl. Wochenschr. 107, 408–413.

Korhonen, H., Syvaöja, E.-L., Ahola-Lutilla, H., Sivela, S., Kopola, S., Kosunen, T.U., 1995. Bactericidal effect of bovine normal and immune serum, colostrum and milk against Helicobacter pylori. J. Appl. Bacteriol. 78, 655–662.

Korhonen, H., Marnila, P., Gill, H.S., 2000a. Milk immunoglobulins and complement factors. Br. J. Nutr. 84 (Suppl.), 75–80.

Korhonen, H., Marnila, P., Gill, H.S., 2000b. Bovine milk antibodies for health. Br. J. Nutr. 84 (Suppl.), 135–146.
Kruse, V., 1970. Yield of colostrum and immunoglobulin in cattle at the first milking after parturition. Anim. Prod. 12, 619–626.

Kuroki, M., Ohta, M., Ikemori, Y., Icatlo, F.C., Jr., Kobayashi, C., Yokoyama, H., Kodama, Y., 1997. Field evaluation of chicken egg yolk immunoglobulins specific for bovine rotavirus in neonatal calves. Arch. Virol. 142, 843–851.

Kühlmann, R., Wiedermann, V., Schmidt, P., Wanke, R., Linckh, E., Lösch, U., 1988. Chicken egg antibodies for prophylaxis and therapy of infectious intestinal diseases. I. Immunization and antibody determination. J. Vet. Med. B 35, 610–616.

Kweon, C.H., Kwon, B.J., Woo, S.R., Kim, J.M., Woo, G.H., Son, D.H., Hur, W., Lee, Y.S., 2000. Immunoprophylactic effect of chicken egg yolk immunoglobulin (IgY) against porcine epidemic diarrhea virus (PEDV) in piglets. J. Vet. Med. Sci. 62, 961–964.

Larrick, J.W., Yu, L., Chen, J., Jaiswal, S., Wycoff, K., 1998. Production of antibodies in transgenic plants. Res. Immunol. 149, 603–608.

Lee, K.A., Chang, S.K., Lee, Y.J., Lee, J.H., Koo, N.S., 2002. Acid stability of anti-Helicobacter pylori IgY in aqueous polyol solution. J. Biochem. Mol. Biol. 35, 488–493.

Le Jan, C., 1996. Cellular components of mammary secretions and neonatal immunity: a review. Vet. Res. 27, 403–417.

Kuroki, M., Ohta, M., Ikemori, Y., Icatlo, F.C., Jr., Kobayashi, C., Yokoyama, H., Kodama, Y., 1997. Field evaluation of chicken egg yolk immunoglobulins specific for bovine rotavirus in neonatal calves. Arch. Virol. 142, 843–851.

Kühlmann, R., Wiedermann, V., Schmidt, P., Wanke, R., Linckh, E., Lösch, U., 1988. Chicken egg antibodies for prophylaxis and therapy of infectious intestinal diseases. I. Immunization and antibody determination. J. Vet. Med. B 35, 610–616.

Kweon, C.H., Kwon, B.J., Woo, S.R., Kim, J.M., Woo, G.H., Son, D.H., Hur, W., Lee, Y.S., 2000. Immunoprophylactic effect of chicken egg yolk immunoglobulin (IgY) against porcine epidemic diarrhea virus (PEDV) in piglets. J. Vet. Med. Sci. 62, 961–964.

Larrick, J.W., Yu, L., Chen, J., Jaiswal, S., Wycoff, K., 1998. Production of antibodies in transgenic plants. Res. Immunol. 149, 603–608.

Lee, K.A., Chang, S.K., Lee, Y.J., Lee, J.H., Koo, N.S., 2002. Acid stability of anti-Helicobacter pylori IgY in aqueous polyol solution. J. Biochem. Mol. Biol. 35, 488–493.

Le Jan, C., 1996. Cellular components of mammary secretions and neonatal immunity: a review. Vet. Res. 27, 403–417.

Le Rousic, S., Klein, N., Houghton, S., Charleston, B., 2000. Use of colostrum from rotavirus-immunised cows as a single feed to prevent rotavirus-induced diarrhea in calves. Vet. Rec. 147, 160–161.

Levieux, D., Ollier, A., 1999. Bovine immunoglobulin G, b-lactoglobulin, a-lactoalbumin and serum albumin in colostrum and milk during the early post partum period. J. Dairy Res. 66, 421–430.

Lindahl, M., 1989. Binding of F41 and K99 fimbriae of enterotoxigenic Escherichia coli to glycoproteins from bovine and porcine colostrum. Microbiol. Immunol. 33, 373–379.

Linder, L.E., Shockman, G.D., Sund, M.L., 1991. Determination of non-immune binding of immunoglobulin G to Staphylococcus aureus by enzyme-linked immunosorbent assays. J. Immunol. Methods 145, 241–246.

Lindström, P., Paulsson, M., Nylander, T., Elofsson, U., Lindmark-Mansson, H., 1994. The effect of heat treatment on bovine immunoglobulins. Milchwissenschaft 49, 67–71.

Liessner, R., Schmidt, H., Karch, H., 1996. A standard immunoglobulin preparation produced from bovine colostra shows antibody reactivity and neutralization activity against Shiga-like toxins and EHEC-hemolysin of Escherichia coli O157:H7. Infection 24, 378–383.

Loimaranta, V., Carlen, A., Olsson, J., Tenuovo, J., Syvaoja, E.L., Korhonen, H., 1998. Concentrated bovine colostral whey proteins from Streptococcus mutans/Strep. sobrinus immunized cows inhibit the adherence of Strep. mutans and promote the aggregation of mutans streptococci. J. Dairy Res. 65, 599–607.

Lucas, F., Corthier, G., 1991. The receptors for bacterial enterotoxins. Ann. Rech. Vet. 22, 127–145.

Lyerly, D.M., Krivan, H.C., Wilkins, T.D., 1988. Clostridium difficile: its disease and toxins. Clin. Microbiol. Rev. 1, 1–18.

Ma, J.K., Hiatt, A., Hein, M., Vine, N.D., Wang, F., Stabila, P., van Dolleweerd, C., Mostov, K., Lehner, T., 1995. Generation and assembly of secretory antibodies in plants. Science 268, 716–719.

Macpherson, A.J., Hunziker, L., McCoy, K., Lamarre, A., 2001. IgA responses in the intestinal mucosa against pathogenic and nonpathogenic microorganisms. Microbes Infect. 3, 1021–1035.

Mainil, J., 1999. Shiga/verocytotoxins and Shiga/verotoxigenic Escherichia coli in animals. Vet. Res. 30, 235–257.

Marquardt, R.R., Jin, L.Z., Kim, J.W., Fang, L., Frohlich, A.A., Baidoo, S.K., 1999. Passive protective effect of egg-yolk antibodies against enterotoxigenic Escherichia coli K88+ infection in neonatal and early-weaned piglets. FEMS Immunol. Med. Microbiol. 23, 283–288.

McCleod, R.E., Gregory, S.A., 1984. Resistance of bovine colostral anti-cholera toxin antibody to in vitro and in vivo proteolysis. Infect. Immun. 44, 474–478.

McGuire, T.C., Pfeiffer, N.E., Weikel, J.M., Bartsch, R.C., 1976. Failure of colostral immunoglobulin transfer in calves dying from infectious diseases. J. Am. Vet. Med. Assoc. 169, 713–718.

Meller, D.J., Murray, L., 1986. Making the most colostrum at lambing. Vet. Rec. 118, 351–353.

Mestecky, J., Lue, C., 1991. Selective transport of IgA. Cellular and molecular aspects. Gastroenterol. Clin. N. Am. 20, 441–471.

Mine, Y., Kovacs-Nolan, J., 2002. Chicken egg yolk antibodies as therapeutics in enteric infectious disease: a review. J. Med. Food 5, 159–169.
Perl, S., Liberboim, M., Harmelin, A., Brenner, J., 1995. Anaemia in lambs caused by feeding bovine colostrum – clinical and pathological findings. Isr. J. Vet. Med. 50, 61–63.

Petschow, B.W., Talbott, R.D., 1994. Reduction in virus-neutralizing activity of a bovine colostrum immunoglobulin concentrate by gastric acid and digestive enzymes. J. Paediatr. Gastroenterol. Nutr. 19, 228–235.

Pisarska, A., Stefaniak, T., Poplewski, M., Przewoźny, M., Ratajski, R., Polak, A., Nowacki, W., 2002. Transfer of maternal passive immunity to kids in goat herd. Pol. J. Vet. Sci. 5, 251–255.

Quigley, J.D. III, 2002. Effects of spray-dried whole egg and biotin in calf milk replacer. J. Dairy Sci. 85, 198–203.

Quigley, J.D. III, Martin, K.R., Dowlen, H.H., 1995. Concentrations of trypsin inhibitor and immunoglobulins in colostrum of Jersey cows. J. Dairy Sci. 78, 1573–1577.

Rea, D.E., Tyler, J.W., Hancock, D.D., Besser, T.E., Wilson, L., Krytenberg, D.S., Sanders, S.G., 1996. Prediction of calf mortality by use of tests for passive transfer of colostral immunoglobulin. J. Am. Vet. Med. Assoc. 208, 2047–2049.

Rivier, D., Sobotka, J., 1978. Protective effect of a rabbit immune serum administered orally to rats infected by human pathogenic strain of E. coli. Exp. Cell Biol. 46, 277–288.

Roos, N., Mahe, S., Benamouzig, R., Sick, H., Rautureau, J., 1995. 15N-labeled immunoglobulins from bovine colostrum are partially resistant to digestion in human intestine. J. Nutr. 125, 1238–1244.

Rzedzicki, J., Wernicki, A., 1994. The influence of colostral leukocytes on the course of an experimental Escherichia coli infection and serum antibodies in neonatal calves. Vet. Immunol. Immunopathol. 35, 275–288.

Riedel-Caspari, G., 1993. The influence of colostral leukocytes on the course of an experimental Escherichia coli infection and serum antibodies in neonatal calves. Vet. Immunol. Immunopathol. 35, 275–288.

Riederer, D., Domingo, R., Sandhu, J., 1997. Oral delivery of antibodies. Future pharmacokinetic trends. Clin. Pharmacokinet. 32, 313–323.

Riedel-Caspari, G., Schmidt, F.-W., 1991. The influence of colostral leukocytes on the immune system of the neonatal calf. II. Effects on passive and active immunization. Dtsch. Tierärztl. Wochenschr. 98, 190–194.

Rivier, D., Sobotka, J., 1978. Protective effect of a rabbit immune serum administered orally to rats infected by human pathogenic strain of E. coli. Exp. Cell Biol. 46, 277–288.

Roos, N., Mahe, S., Benamouzig, R., Sick, H., Rautureau, J., 1995. 15N-labeled immunoglobulins from bovine colostrum are partially resistant to digestion in human intestine. J. Nutr. 125, 1238–1244.

Rzedzicki, J., Wernicki, A., 1994. The influence of colostral leukocytes on the course of an experimental Escherichia coli infection and serum antibodies in neonatal calves. Vet. Immunol. Immunopathol. 35, 275–288.

Sarker, S.A., Casswall, T.H., Juneja, L.R., Hoq, E., Hossain, I., Fuchs, G.J., Hammarstrom, L., 2001. Randomized, placebo-controlled, clinical trial of hyperimmunized chicken egg yolk immunoglobulin in children with rotavirus diarrhea. J. Pediatr. Gastroenterol. Nutr. 32, 19–25.

Schade, R., Hlinak, A., 1996. Egg yolk antibodies, state of the art and future prospects. ALTEX 13, 5–9.

Schmidt, L.S., Nyachoti, C.M., Slominski, B.A., 2003. Nutritional evaluation of egg byproducts in diets for early-weaned pigs. J. Anim. Sci. 81, 2270–2278.

Sharp, J.M., Doran, P.M., 2001. Characterization of monoclonal antibody fragments produced by plant cells. Biotechnol. Bioeng. 73, 338–346.

Sheldrake, R.F., Husband, A.J., 1985. Immune defences at mucosal surfaces in ruminants. J. Dairy Res. 52, 599–613.

Shibata, I., Ono, M., Mori, M., 2001. Passive protection against porcine epidemic diarrhea (PED) virus in piglets by colostrum from immunized cows. Vet. Med. Sci. 63, 655–658.

Shimizu, M., Hashimoto, K., Ozeki, M., Tsuda, K., Hatta, H., 1992. Molecular stability of chicken and rabbit immunoglobulin G. Biosci. Biotechnol. Biochem. 56, 270–274.

Shimizu, M., Miwa, Y., Hashimoto, K., Gojo, A., 1993a. Encapsulation of chicken egg yolk immunoglobulin G (IgY) by liposomes. Biosci. Biotechnol. Biochem. 57, 1445–1449.

Shimizu, M., Nagashima, H., Hashimoto, K., 1993b. Comparative studies in molecular stability of immunoglobulin G from different species. Comp. Biochem. Physiol. B 106, 255–261.

Shimizu, M., Nagashima, H., Suzuki, T., 1994. Egg yolk antibody (IgY) stability in aqueous solution with high sugar concentration. J. Food Sci. 59, 763–772.

Sivula, N.J., Ames, T.R., Marsh, W.E., Werdin, R.E., 1996. Descriptive epidemiology of morbidity and mortality in Minnesota dairy heifer calves. Prev. Vet. Med. 27, 155–171.

Snodgrass, D.R., Fitzgerald, T., Campbell, I., Scott, F.M.M., Browning, G.F., Miller, D.L., Herring, A.J., Greenberg, H.B., 1990. Rotavirus serotypes 6 and 10 predominate in cattle. J. Clin. Microbiol. 28, 504–507.
Yuehuei, H., Friedman, R.J. (Ed.), 2000. Handbook of Bacterial Adhesion. Principles, Methods and Applications. Humana Press Inc., Totowa, New Jersey, pp. 17–551.
Zuniga, A., Yokoyama, H., Albicker-Rippinger, P., Eggenberger, E., Bertschinger, H.U., 1997. Reduced intestinal colonisation with F18-positive enterotoxigenic *Escherichia coli* in weaned pigs fed chicken egg antibody against the fimbriae. FEMS Immunol. Med. Microbiol. 18, 153–161.