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# CLINICAL MICROBIOLOGY REVIEWS

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and Jose R. Cruz ..... 12-29

*Summary: Appropriate selection of donors, use of sensitive screening tests, and the application of a mandatory quality assurance system are essential to maintain the safety of the blood supply. Laws, decrees, norms, and/or regulations covering most of these aspects of blood transfusion exist in 16 of the 17 countries in Latin America that are the subject of this review. In 17 countries, there is an information system that, although still incomplete (there are no official reports on adverse events and incidents), allows us to establish progress made on the status of the blood supply since 1993. Most advances originated in increased screening coverage for infectious diseases and better quality assurance. However, in 2001 to 2002, tainted blood may have caused infections in 12 of the 17 countries; no country reached the number of donors considered adequate, i.e., 5% of the population, to avoid blood shortages, or decreased significantly the number of blood banks, although larger blood banks are more efficient and take advantage of economies of scale. In those years, paid donors still existed in four countries and replacement donors made up >75% of the blood donors in another eight countries. In addition, countries did not report the number of voluntary donors who were repeat donors, i.e., the healthiest category. In spite of progress made, more improvements are needed.*

**Allergy and Dermatophytes.** Judith A. Woodfolk ..... 30-43

*Summary: Tinea pedis (athlete's foot) and onychomycosis (infection of the toenails) caused by the dermatophyte fungus Trichophyton are highly prevalent in adults. Several Trichophyton allergens have been identified based on elicitation of immunoglobulin E antibody-mediated immediate-hypersensitivity (IH) responses. Evidence of an etiologic role for Trichophyton in*

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asthma in some subjects with IH and chronic dermatophytosis is provided by bronchial reactivity to Trichophyton. Improvement of asthma after systemic antifungal treatment corroborates this link. A unique feature of Trichophyton allergens is the ability of the same antigen to elicit delayed-type hypersensitivity (DTH) in individuals who lack IH reactivity. Delayed responses appear to confer protection, while IH responses do not, based on the association with acute versus chronic skin infection. The amino acid sequence identity of Trichophyton allergens with diverse enzyme families supports a dual role for these proteins in fungal pathogenesis and allergic disease. Characterizing the immunologic properties of Trichophyton allergens and defining immune mechanisms which drive dichotomous responses are pivotal to understanding the dermatophyte-allergy relationship. Recent studies have identified DTH-associated major T-cell epitopes which could facilitate the development of peptide vaccines. Characterization of additional molecular targets by using new techniques may aid not only in the eradication of infection but also in the resolution of allergic symptoms.

Surf

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*Summary: Aspergillus infections are occurring with an increasing frequency in transplant recipients. Notable changes in the epidemiologic characteristics of this infection have occurred; these include a change in risk factors and later onset of infection. Management of invasive aspergillosis continues to be challenging, and the mortality rate, despite the use of newer antifungal agents, remains unacceptably high. Performing molecular studies to discern new targets for antifungal activity, identifying signaling pathways that may be amenable to immunologic interventions, assessing combination regimens of antifungal agents or combining antifungal agents with modulation of the host defense mechanisms, and devising diagnostic assays that can rapidly and reliably diagnose infections represent areas for future investigations that may lead to further improvement in outcomes.*

Me

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**Pathway to Synthesis and Processing of Mycolic Acids in Mycobacterium tuberculosis.** Kuni Takayama, Cindy Wang, and Gurdyal S. Besra .....

81-101

*Summary: Mycobacterium tuberculosis is known to synthesize  $\alpha$ -, methoxy-, and keto-mycolic acids. We propose a detailed pathway to the biosynthesis of all mycolic acids in M. tuberculosis. Fatty acid synthetase I provides C<sub>20</sub>-S-coenzyme A to the fatty acid synthetase II system (FAS-IIA). Modules of FAS-IIA and FAS-IIB introduce cis unsaturation at two locations on a growing meroacid chain to yield three different forms of cis,cis-diunsaturated fatty acids (intermediates to  $\alpha$ -, methoxy-, and keto-meroacids). These are methylated, and the mature meroacids and carboxylated C<sub>26</sub>-S-acyl carrier protein enter into the final Claisen-type condensation with polyketide synthase-13 (Pks13) to yield mycolyl-S-Pks13. We list candidate genes in the genome encoding the proposed dehydrase and isomerase in the FAS-IIA and FAS-IIB modules. We propose that the processing of mycolic acids begins by transfer of mycolic acids from mycolyl-S-Pks13 to D-mannopyranosyl-1-phosphoheptaprenol to yield 6-O-mycolyl- $\beta$ -D-mannopyranosyl-1-phosphoheptaprenol and then to trehalose 6-phosphate to yield phosphorylated trehalose monomycolate (TMM-P). Phosphatase releases the phosphate group to yield TMM, which is immediately transported outside the cell by the ABC transporter. Antigen 85 then catalyzes the transfer of a mycolyl group from TMM to the cell wall arabinogalactan and*

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to other TMMs to produce arabinogalactan-mycolate and trehalose dimycolate, respectively. We list candidate genes in the genome that encode the proposed mycolyltransferases I and II, phosphatase, and ABC transporter. The enzymes within this total pathway are targets for new drug discovery.

**Surface Proteins of *Streptococcus agalactiae* and Related Proteins in Other Bacterial Pathogens.** Gunnar Lindahl, Margaretha Stålhammar-Carlemalm, and Thomas Areschoug ..... 102-127

*Summary: Streptococcus agalactiae (group B Streptococcus) is the major cause of invasive bacterial disease, including meningitis, in the neonatal period. Although prophylactic measures have contributed to a substantial reduction in the number of infections, development of a vaccine remains an important goal. While much work in this field has focused on the S. agalactiae polysaccharide capsule, which is an important virulence factor that elicits protective immunity, surface proteins have received increasing attention as potential virulence factors and vaccine components. Here, we summarize current knowledge about S. agalactiae surface proteins, with emphasis on proteins that have been characterized immunochemically and/or elicit protective immunity in animal models. These surface proteins have been implicated in interactions with human epithelial cells, binding to extracellular matrix components, and/or evasion of host immunity. Of note, several S. agalactiae surface proteins are related to surface proteins identified in other bacterial pathogens, emphasizing the general interest of the S. agalactiae proteins. Because some S. agalactiae surface proteins elicit protective immunity, they hold promise as components in a vaccine based only on proteins or as carriers in polysaccharide conjugate vaccines.*

**Mechanical Transmission of Human Protozoan Parasites by Insects.** Thaddeus K. Graczyk, Ronald Knight, and Leena Tamang ..... 128-132

*Summary: The filthy breeding habits, feeding mechanisms, and indiscriminate travel between filth and food make some groups of synanthropic insects such as nonbiting flies and cockroaches efficient vectors of human enteric protozoan parasites. Twenty-one species of filth flies have been listed by regulatory agencies concerned with sanitation and public health as causative agents of gastrointestinal diseases based on synanthropy, endophily, communicative behavior, and strong attraction to filth and human food. Outbreaks and cases of food-borne diarrheal diseases in urban and rural areas are closely related to the seasonal increase in abundance of filth flies, and enforced fly control is closely related to reductions in the occurrence of such diseases. Mechanical transmission of human parasites by nonbiting flies and epidemiological involvement of other synanthropic insects in human food-borne diseases have not received adequate scientific attention.*

**Options for Field Diagnosis of Human African Trypanosomiasis.** François Chappuis, Louis Loutan, Pere Simarro, Veerle Lejon, and Philippe Büscher ..... 133-146

*Summary: Human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense or T. b. rhodesiense remains highly prevalent in several rural areas of sub-Saharan Africa and is lethal if left untreated. Therefore, accurate tools are absolutely required for field diagnosis. For T. b. gambiense HAT, highly sensitive tests are available for serological screening but the sensitivity of parasitological confirmatory tests remains insufficient and needs to be improved. Screening for T. b. rhodesiense infection still relies on clinical features in the absence of serological tests available for field use. Ongoing research is opening perspectives for a new generation of field diagnostics. Also essential for both forms of HAT is accurate determination of the disease stage because of the high toxicity of melarsoprol, the drug most widely used during the neurological stage of the illness. Recent studies have confirmed the high accuracy of raised immunoglobulin M levels in the cerebrospinal fluid for the staging of T. b. gambiense HAT, and a promising simple assay (LATEX/IgM) is being tested in the field. Apart from the urgent need for better tools for the field diagnosis of this neglected disease, improved access to diagnosis and treatment for the population at risk remains the greatest challenge for the coming years.*

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