

Telemicrobiology for Mission Support in the Field of Infectious Diseases

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ABSTRACT

Infectious diseases are among the most common diseases in missions abroad. Their diagnosis requires special procedures and expertise, both provided by the microbiological field laboratories. In order to support the diagnostic process by means of telemedicine, a modification of the standard telemedical workstation, i.e. a module “telemicrobiology” with special equipment, camera and software, has been designed and validated. This module, meanwhile installed in six operational theaters, has stood the test in routine practice. It enables the transmission of high-quality static images of microscopic specimens or overgrown nutrient media in a matter of seconds. The telemedical inclusion of experts into diagnostic analysis improves diagnostic specificity by avoiding false positive results and, particularly in medical parasitology, allows a treatment-essential diagnosis without dispatch of specimens to Germany. In bacteriology, telemicrobiology allows the control of the entire diagnostic process by the expert workstation even with a mere technical staff on site.

1.0 INFECTION MEDICINE AND INFECTION DIAGNOSIS IN THEATER

Soldiers in missions abroad are at greater risk of infection for several reasons. They are, for example, particularly exposed to infectious animals, such as mosquitos or rodents, acting as reservoir hosts and vehicles or vectors of pathogenic organisms. The supply of food and drinking water is a critical field decisively determining the incidence of gastrointestinal infections. Sexually transmissible diseases are of great importance as well. According to experience, a considerable percentage of the deployed troops falls under the risk exposure rate. The individual disposition for infections may be increased by stress and high physical strain. The incidence of wound infections primarily depends on the mission profile. With bacterial infections, depending on the country of deployment, also unusual resistance behavior of the pathogens will occur because numerous infectious pathogens – e.g. pathogens of respiratory infections – spread extremely well within the military community living in cramped conditions. In missions of the US Forces in the recent years, well-documented with respect to epidemiology, the weekly incidence of infectious diseases was always one of the highest numbers when compared to other diagnosis categories with the gastrointestinal and respiratory infections – differing in predominance – always forming the highest number in statistics. The incidence of infections by local endemic infectious pathogens has to be expected as well. Of course, this especially applies to the local population getting medical treatment, as required, within the scope of humanitarian assistance. Moreover, the endemic infectious diseases of the respective country of origin have to be taken into consideration when giving medical support to soldiers of friendly forces. Infection medicine, as an interdisciplinary field affecting numerous special clinical fields, as well as infection epidemiology are primarily based on the laboratory diagnosis of the microbiological field laboratories.

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According to the guiding principle of the Surgeon General, Bundeswehr and Chief of Staff, Medical Service, the soldiers, when suffering from disease, injury or wound in missions abroad, are entitled to high-quality medical support achieving results equivalent to those obtained by a treatment in Germany. This result-oriented guiding principle does not necessarily mean a one-to-one transference of the medical practice in Germany to the country of deployment. In general, the conditions on site would not permit such an approach especially not in technically sophisticated special fields – which include medical microbiology. Thus, in the specific situation of the mission abroad, the special field relies on methods taking the technical feasibility into consideration as well as the objective requested by the guiding principle. The operation of the field laboratories is based on a pool of personnel which, for reasons of sustainability, requires a considerably greater number of specialists than those working in specialized microbiological facilities. This inevitably results in the fact that – depending on the individual specialization – the required special expertise in all sections of microbiology (bacteriology, virology, parasitology) cannot always be present on site. For these reasons, in large parts of the diagnostic field, in the past the time-consuming transportation of specimens to Germany was the only possibility to make specialized microbiological expertise available also in missions abroad well. Thus, the objective of a project initiated in the Central Institute in Coblenz in 2003 was to evaluate to what extent telemedical procedures are suitable for rapid mission support in medical microbiology. This was a new approach since telemedical technology has been validated only once for this special field up to now in a very limited field of application, i.e. the transmission of microscopic photographs/images of Gram specimens only (McLaughlin et al, 1998).

This is a report on the establishment and implementation of a specific module “telemicrobiology”, a variant of the telemedical workstation (TW) introduced into the Medical Service as well as on the validation results and the application experience gained in daily routine practice.

2.0 TELEMEDICINE IN MISSIONS ABROAD

Telemedicine means the “execution of medical tasks by using electronic teletransmission for the transfer of medical data“. In general, the transmitted data are images. According to another definition, telemedicine is the “use of information and communication technologies to make medical services available irrespective of location and time“. The Bundeswehr Medical Service already uses telemedical applications in various fields. At present, more than one hundred TWs are in service. They are located in the medical facilities of seagoing vessels as well as in field hospitals, mobile surgical hospitals or medical centers. Experience has been gained especially with applications in the special fields of surgery, radiology, dentistry or dermatology. The German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt = DLR, Cologne) ensures the technical support in the field of telemedicine.

2.1 The Microbiological Field Laboratory in Missions Abroad

The important role of the laboratory in an operating scenario is undisputed in international military medicine. One of the consensuses developed during the Military Public Health Laboratory Symposium held in Washington in 1999 was that rapid access to the state-of-the-art diagnosis of infectious diseases is necessary at all levels of military health services, i.e. also in missions abroad (Gaydos, 2000).

Besides the diagnoses oriented to individual treatment with the aim to come to quick therapeutic decisions, surveillance with the aim to identify outbreak situations at an early stage to be able to rapidly implement actions interrupting the infectious chain, is at least of equal importance.

After all, the laboratories represent the lowest diagnostic level of microbiological defense. Therefore, they have to be in the position where they do not overlook the incidence of infectious diseases by potential B agents and/or are able to produce findings suspecting such agents; their verification would then be the duty of experts in biological defense.

Due to technical sophistication, the realization of clinical-microbiological diagnoses in missions abroad is subject to certain limits. The microbiological field laboratory is housed in a standard container or a medical facility with built-in laboratory devices, e.g. including a laminar airflow cabin, Class 2. The technical equipment is suitable to conduct three groups of methods including various microscopic procedures to verify bacteria, especially acid-proof rod-shaped bacteria, for malaria diagnosis and to verify parasites in stool or tissue. The culture techniques deal with the non-selective culturing of bacteria from variable investigational materials, the selective cultivation of enteritis pathogens as well as the antimicrobial sensibility test. In serology, enzyme immune tests and immunofluorescence tests can be conducted. As of last year, within the scope of the field laboratory standardization and quality assurance concept, we have established the possibility to conduct rapid immunochromatographic analyses on a larger scale.

2.2 Options of Telemedical Mission Support in Medical Microbiology

In general, telemedical applications are based on image transmission techniques. Therefore, in the field of medical microbiology, all techniques suitable for visual assessment and, thus, for image transmission are potentially suitable for telemedical evaluation. This means the assessment of microscopic preparations, bacteriological cultures and – in rare cases – also of macroscopic objects (e.g. excreted worms or worm components, Ectoparasites). In culture bacteriology, the control of the entire sequence of the diagnostic process is primarily based on such visually evaluable findings. The typical appearance of colonies grown on nutrient media, for example, is used to decide on further diagnostic steps (e.g. preparation of stained microscopic specimens, application of a biochemical identification system. In parasitology, a definitive diagnosis can already be made in most cases by microscopy alone. For this reason, this specific field is extremely suitable for telemedical support.

2.3 Technical Concept of the TW Module “Telemicrobiology”

In addition to the standard equipment of a TW, comprising a PC and the standard periphery, special auxiliary equipment, comprising a standard substage microscope with fluorescence device, a plate microscope as well as two cold-light sources for illumination of the nutrient media plates to be photographed, was defined for medical microbiology with respect to the telemedical options described above. Both microscopes are provided with adapters for the high-resolution digital onechip camera with 1360x1024 image points to take static images. By means of this camera, a live image can be displayed on the monitor, which can be optimally adjusted by the investigator prior to taking the image. Moreover, the special image processing, transmission and archiving software (DISKUS) of Messrs. Hilgers is used which was developed especially for this type of image transmission and which has predominantly been used in histopathology so far. The software in the background automatically controls the establishment of a link and the standardized image transmission while the investigator continues microscoping and taking images. The transmission per image takes about 10 - 30 seconds. The software ensures an absolutely identical image display at the transmitting and the receiving end (WYSIWYG principle) which makes it possible to discuss structures of interest in the teleconference by using a superimposed coordinate grid. Prior to taking the image, the luminosity and brilliance settings of the live image can be adjusted with respect to. Marking and labeling is possible as well. The co-transmission of the adjusted lens magnification enables automatic measuring operation at the receiving end, e.g. measuring the diameter of an inhibiting areola in millimeters simply by drawing a graphical line between the desired measuring points with the mouse. Furthermore, the program provides other useful image processing and discussions tools.

2.4 Validation of the TW Module “Telemicrobiology”

2.4.1 Quality of Images

First, the display quality of essential morphological characteristics was assessed using microscopic and macroscopic images from bacteriology and parasitology. When taking images of overgrown nutrient

media, the obtainable resolution of the images arriving at the receiving end permitted the fine detail display of all essential colony properties, such as surface characteristics, hemolysis behavior, color, etc. In microscopic diagnosis, the display of parasitological structures, such as intestinal protozoa or worm ova, was brilliant. In malaria diagnosis, all parasite details required for species diagnosis were transmitted perfectly. This was the case e.g. with the Schüffner's granules of erythrocytes for a *plasmodium vivax* infection (malaria tertiana) and also with the delicate cytoplasm of the signet rings of *plasmodium falciparum*. The display of bacteria in Gram specimens was excellent as well, though bacteria no doubt are the smallest objects still displayable with satisfactory sharpness at the selected camera resolution.

2.4.2 Diagnostic System Performance

The diagnostic system performance was tested in several double blind experimental approaches. An independent chief experimental officer presented without further information prepared specimens to the investigators. The medical assistants (usual basic training without expert knowledge) acting as transmitting users had the task to take images of structures characterized as suspicious and to transmit them to the receiving user for their diagnostic assessment. Experts in the respective special fields (bacteriologist, parasitologist) were acting as receiving user. Some of the results of this study are described below.

2.4.3 Malaria Diagnosis

N = 36 specimens (16 thick and 20 thin blood films) were tested with 16 (6 thick and 10 thin blood films) thereof positive and 20 negative. The transmitting user classified 18 specimens as positive. 16 diagnoses were true positive. Two results were false positive. One species diagnosis could not be given.

The expert assessed 16 specimens as positive. All definitive diagnoses were true positive. According to the transmitted images, the receiving user could not differentiate correctly between the diagnosis of malaria tropica and of malaria non-tropica in ten of ten thin blood film specimens. Correct species diagnoses could be given for eight of ten specimens. With the two other specimens, no differentiation between *plasmodium vivax* and *plasmodium ovale* could be made; however, even in usual parasitological diagnoses often a clear differentiation is not possible.

2.4.4 Parasitological Stool Diagnosis

40 specimens were examined with n = 90 parasitological findings and/or species diagnoses to be made out. The transmitting user identified 63 findings (70 %) and gave correct species diagnoses in 53 cases (84.1 %). When limiting the evaluation to the clinically relevant (pathogenic) species only, the rate of correct species diagnoses could be increased from 77.4 % (transmitting user) to 88.7 % (expert). The expert detected 68 findings from the transmitted images with all species data being correct. In 50 negative reference specimens, the transmitting user identified in 2 cases suspicious structures not confirmed by the expert.

2.4.5 Liquor Diagnosis

A total of 20 Gram-stained specimens was evaluated to which cells and various bacteria had been added within the scope of preparation. Suspensions in logarithmic dilution series were prepared of each strain of bacteria so that only very few bacteria could be verified in the last degree of dilution. Only one strain per liquor was used. The transmitting user detected 18 of the 20 specimens as positive, 2 as negative. In one case, these were pneumococci in degree of dilution 3, in the other case meningococci in degree of dilution 4. The receiving user confirmed the 18 positive specimens. In 3 cases, the receiving user only wanted to decide after transmission of additional images (e.g. since only sporadic structures were detectable). The receiving user also could not identify bacterial structures in the transmitted images of the false negative specimens.

The morphologic classification of the detected bacteria in rods or cocci, Gram-positive or Gram-negative staining behavior was correct in all 18 cases with the transmitting and the receiving user.

2.4.6 Gram Specimens of Various Materials

20 Gram-stained specimens had to be investigated in this sub-collective. The task was to indicate the predominant germs according to morphologic criteria. A total of 34 germ findings was expected. The transmitting user detected 32 (94.1 %) of the relevant findings while Gram-negative rods were overlooked in two specimens. Based on the transmitted images, the expert detected 33 findings (97 %). In one specimen, corynebacteria were overlooked which had been detected by the transmitting user.

The transmitting user determined 30 negative reference specimens as true-negative. All findings were confirmed by the receiving user (experts) so that the total specificity of the bacterioscopic diagnosis was 100 %.

2.4.7 Gram Specimens from Cultures

A total of 19 Gram specimens were prepared from fresh microbic cultures which had to be microscoped. Again, the task was to characterize the germs according to morphologic criteria (cocci, rods, Gram staining behavior).

The transmitting user was correct in characterizing 18 of the 19 strains (94.7 %). In one case, Gram-negative diplococci were mistaken for Gram-positive cocci. The expert gave a correct interpretation of all 19 specimens (100 %).

2.4.8 Assessment of Overgrown Nutrient Media

26 different strains of bacteria were inoculated onto a total of 40 culture plates (different media). The plates were incubated for 1 to 2 days prior to the test. The transmitting end had the task to depict by means of the reflected light microscope and the cold-light source as much as possible of morphologic details of the culture plates, such as surface of the colonies, hemolysis behavior, swarm behavior etc. and to transmit them to the receiving user. The latter had to assess the colonies and could request by teleconference additional properties, such as odor, from the transmitting user. As a result, the direction of diagnosis had to be determined as it is used in bacteriology as basis for further diagnostic procedures (e.g. indication of several possibilities or group diagnosis coming into consideration).

The hit rate of this test was 100 %, i.e. the correct diagnosis direction was given for all strains.

2.4.9 Validation Results

The main validation objective was to determine the TW contribution to improved diagnosis in medical microbiology under the conditions in missions abroad. An approach simply testing technical characteristics, e.g. by determining the reproduceability at the transmitting and the receiving end, would have been unsatisfactory since the 100 % reproduceability of measuring results does not necessarily reflect the fact that the diagnosis is entirely correct. This would only be the case if other factors, e.g. the expertise of the transmitting user, were only of minor influence on diagnosis. Yet, when transmitting static images in bacteriology and parasitology, the expertise of the transmitting user is of decisive importance for he cannot transmit what he does not notice. The collected data clearly showed this fact. For example, the total sensitivity of diagnosis (number of true positive diagnoses in relation to the number of all detectable diagnoses) was not 100 % but between 72 % and 100 % depending on the sub-collective, thus reflecting the fact that findings not detected by the transmitting user could not arrive at the receiving user either. The expert occasionally detected findings overlooked by the transmitting user, yet, only when they were more or less detectable on the images (e.g. stool specimen with several parasite species but with only one

species detected by the transmitting user). The decisive advantage of telemedical support, however, was the considerably higher percentage of correct species diagnoses through expert participation. The fact that only a few clinically relevant findings were overlooked is of great importance as well. In the diagnosis of potentially fatal malaria, all diagnoses were correct. However, without telemedical expert participation, the certain species diagnosis and thus the decisive differentiation between malaria tropica and malaria non-tropica would not have been possible. In liquor diagnosis, the sensitivity of the expert diagnosis was 90 %. It has to be taken into consideration, though, that the conditions were artificial by preparing dilution series of the bacteria; both false negative specimens referred to higher degrees of dilution with only a few germs occurring. Moreover, the cell picture did not correspond to that of bacterial meningitis so that important additional verification was lacking. Microscopic diagnoses in the expert laboratory also rarely yield a sensitivity of 100 %. On the contrary, the values obtained already reflect a high sensitivity. Finally, even the deployment of a medical officer on site would hardly result in a cross-sectional improvement of the values since physicians in general also do not have satisfactory routine experience in all sub-branches of microbiology. Another advantage of telemedical support is that an optimum total sensitivity of 100 % could be obtained in definitive expert diagnosis. The expert could clear away false positive findings or unfounded suspicious findings of the transmitting users. In malaria diagnosis, for two (10 %) suspicious findings in negative specimens by the transmitting ends a negative diagnosis could be made by the expert. This is particularly important considering the fact that the uncertain exclusion of malaria inevitably results in a therapy which would have been false in these cases, not to mention the false epidemiologic situation picture that might have been induced.

2.5 Experience in Routine Practice

In November 2003, the first telemicrobiology system was implemented in the Field Hospital Prizren (KFOR) where it is operating in daily routine. In October 2004, the installation in the Field Hospital Kabul (ISAF) followed. The implementations with EUFOR (Rajlovac) an ISAF Mazar E Sharif, Kunduz and Feyzabad followed through the years as well as the two hospital-ships. With KFOR, the microbiological field laboratory has one post for a medical assistant, and ISAF has an additional specialist. The focus of the telemicrobiological application with KFOR is on bacteriology. All overgrown nutrient media are assessed by telemedicine, and the further diagnostic process is controlled based on the instructions of the expert. With ISAF, the parasitologic expert support has been the main field of application up to now. It proved to be extremely helpful especially in the diagnosis of endemic parasitoses, such as malaria or leishmaniasis, with several cases of dermal leishmaniasis identified by telemicroscopy. The telemedical link is used every day including the weekend. After establishment of the video conference link, the DISKUS program is started at the receiving as well as the transmitting end, and the current cases are discussed based on the transmitted images. All telemedical cases are recorded by the assessing expert according to a scheme adapted to the microbiological method of operation. With KFOR, the findings photographed by the medical assistant are provided with the note “validated by telemedicine” and the name of the releasing physician. Apart from rare link failures, quickly eliminated with the assistance of DLR, the technical equipment operated without any problem. The satellite capacity was always sufficient to transmit the images to Germany quickly. The lead institute in Coblenz offers 24-h accessibility via duty NCO, duty medical assistant and duty physician. The possibility of teleteaching, i.e. the continuous specialized training of deployment forces by the transmission of relevant special information with respect to diagnosis, epidemiology, therapy and prevention of infection diseases, turned out to be a relevant side aspect. The clinicians also have the possibility to contact an expert in Germany by teleconference any time, especially when dealing with problems in antibiotic therapy and epidemiology. The telemedical tool has proved extremely useful in outbreak management as well.

3.0 TELEMICROBIOLOGY IN THE OVERALL CONCEPT OF A LABORATORY-ASSISTED INFECTION MEDICINE IN MISSIONS ABROAD

The module “telemicrobiology” installed in missions abroad after validation has proven successful in practice. The expectations regarding an additional expertise transfer to the operational theaters have been met. In this way, special microbiological expertise can be made available to the clinician in a mission abroad which otherwise would not be available on site. Under specific preconditions, the implementation of telemicrobiology may result in the situation that the functional control is managed from Germany and only medical assistants are required to post the field laboratory. In this way, the maxim of telemedicine “exportation of expertise instead of exportation of experts” has been realized. This is the first telemicrobiology system in routine operation worldwide. The positive experience has already prompted interest from civil organizations and a first decision on the use and procurement of analogue systems.

Nevertheless, it should be noted that telemicrobiology can only be useful in a well-coordinated overall diagnostic system. It is not a replacement but an additional technique and depends on various preconditions including diagnosis standardization so that results which will undergo visual interpretation may be produced on a methodically standardized and established base. Only then, the expert workstation will be able to interpret, validate and release findings. All image-relevant factors, such as staining techniques, nutrient media used, etc. have to be specified in standard work instructions and have to correspond to the diagnostic routine procedures the expert is used to and which are used by the expert workstation; this is the only way to avoid misinterpretations. The deployment personnel has to be prepared by specific training for this standardized methodology. The necessity of specialized preparation for deployments may also be derived from the fact that, in the transmission of static images, the ability of the deployment personnel to detect suspicious structures in microscopic specimens is a limiting factor. This was also an essential conclusion of McLaughlin et al who validated a telemicrobiology system based on the transmission of Gram-stained specimens (McLaughlin et al., 2000). The Central Institute Coblenz takes this training requirement into account by conducting a three week course for the specialized preparation for deployments with telemicrobiological procedures playing an important role.

Contrary to telemedical applications in other fields of specialization, medical microbiology does not only comprise advice to those responsible on site (“secondary opinion”) but also the functions controlling diagnosis and the responsible release of medical findings (“primary opinion”). Responsibility and right of control on the part of the expert workstation, however, still require administrative regulation.

Finally, problems which cannot be solved on site due to technical reasons (confirmatory diagnosis, molecularbiological procedures, thorough serology etc.) still require backward diagnosis in Germany to

4.0 LITERATURE

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