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Facing highly infectious diseases: new trends and current concepts

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Abstract

A highly infectious disease (HID) that is transmissible from person to person causes life-threatening illness and presents a serious hazard in the healthcare setting and in the community that requires specific control measures. Due to environmental factors, changes in life-style and many other unknown factors, the emergence of such HIDs is becoming more and more likely. As has already been demonstrated during the SARS outbreak, healthcare facilities are likely to be the origin of future HID outbreaks. Preparedness planning will be essential in helping facilities manage future outbreaks of emerging or resurgent infectious diseases. Guidelines have been developed by national and international institutions. To avoid contamination of healthcare workers, the care of HID patients should follow the same infection control rules that are applied to laboratory workers exposed to similar agents. Here, the current knowledge concerning the clinical care of patients with HIDs is reviewed, and specific aspects of the management of such diseases are introduced.

Keywords: Bioterrorism, class 3 and 4 agents, infection control, isolation room, SARS

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Introduction

During recent decades, many new and re-emerging diseases have threatened public health and have posed new challenges to infectious disease specialists worldwide. The expansion of the human population results in a greater proximity to the habitat of wildlife, and a massive urbanization process, both of which facilitate the emergence of new zoonoses and the rapid spread of communicable diseases among humans. Travelling throughout the world in a few hours has become increasingly frequent. This leads to a new epidemiological situation where the risk of worldwide contagion is more and more present, while the preparedness of hospitals in the face of this situation is still at an early stage of development [26]. Imported highly infectious diseases (HIDs) such as Lassa fever [19] and other haemorrhagic fever viruses, have been reported many times in the literature but have seldom been at the origin of an outbreak, except for SARS. Experience shows that the recognition and isolation of a new infectious agent is often followed by reports of a laboratory-acquired infection caused by the new isolate [24]. Among class 3 and 4 agents, laboratory-associated infections have been reported with the agents of epidemic typhus [50], murine typhus [48], Q fever [18], tularaemia [23], pulmonary plague [9], Lassa fever [25], Rocky Mountain Spotted fever [33], melioidosis [38], and with Herpes B virus simiae [16], Hantaan virus [20,24], tick borne encephalitis virus [46], sabia virus [6], West Nile virus [1,2], and vaccine [28]. More recently SARS coronavirus (CoV) was laboratory acquired [27], raising concern with respect to biosafety [32]. Although laboratories that handled class 3 and 4 agents should comply with biosafety regulations, laboratory leakage may occur at any time when working with a known agent, but also when attempting to isolate an unknown infectious agent such as a mimivirus [37]. Infection of a single laboratory worker with a highly infectious agent is likely to be at the origin of an outbreak, especially if the agent has the capability of human-to-human transmission such as happened with the SARS CoV [27]. Terrorist attacks using biological agents are a substantial threat to the safety, health and security of citizens. As the 2001 anthrax attacks illustrated, only a small amount of agent is required to have a tremendous impact in terms of morbidity, cost, and mental health [30]. These consequences would probably have been exponentially greater if the terrorists had utilized an agent that causes a communicable disease, because this could have resulted in the rapid spread of secondary infection [30]. As a consequence, preparedness will be essential in the management of future outbreaks, and networking is an essential approach for success (see Ippolito *et al.* in this issue).

A number of definitions will be useful in preparing readers for this special section concerning Europe's preparedness to face HIDs.

A highly infectious disease (HID), which is transmissible from person to person, causes a life-threatening illness and presents a serious hazard in healthcare settings and in the community, requiring specific control measures [7]. The agents responsible for these diseases are class 3 and 4 agents as defined by the CDC in the 5th edition of the Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual [45].

A highly infectious disease isolation unit (HLIU) is a 'healthcare facility specifically designed to provide safe, secure, high-quality and appropriate care, with optimal infection containment and infection prevention and control procedures for a single patient or small number of patients who have, or who may have, a highly infectious disease' [7].

Levels of biosecurity were first defined for the laboratory according to the assessed risk of transmission to humans and the possible threat. Infectious agents classified as class 2 must be handled at Bio Safety Level (BSL) 2, as must class 3 agents at BSL 3 and class 4 agents at BSL 4 laboratories. To asses this level of biosecurity, guidelines have been drawn up by the CDC in the 5th edition of the BMBL manual [45] and by the WHO in the 2nd edition of the Laboratory Safety manual [47]. Considering the fact that, in some situations, such as cough, the inoculums spread by the patient to whom the employees are exposed are likely to be equivalent to those encountered by a laboratory worker when handling specimens, the care of such patients should be undertaken in BSL 3 or 4 wards to ensure the same level of protection and security for healthcare workers (HCWs) as that for laboratory workers exposed to the same agent. Situations that indicate the use of such a HLIU are those in which class 3 or 4 agents are suspected to be at the origin of the disease. This is obviously also based upon the capability of the agent to achieve human-to-human transmission, and the availability of primary or secondary prophylaxis such as vaccines of effective antimicrobial therapy. The risk group classification of infectious agents for laboratory practice [4,45] does not correspond precisely to the risk group classification for clinical practice, and recommendations for a minimum isolation level of the patient in the healthcare setting will be published elsewhere [8].

Concerning the *isolation room and ward for care of HID patients,* a BSL 3 ward is defined as a ward fulfilling the criteria of a BSL 3 level laboratory [45,49]. Briefly, it is a negative pressure ward with an anteroom and single-bed rooms. The air is high efficiency particulate air (HEPA) filtered and expelled outside; the intake is HEPA filtered; the number of air changes is at least 12 per hour (depending on national law); and depressurization is monitored by an audible and visual device as recommended by the American Institute of Architects [5] and described in the Health Care facility design resource manual published by the Phoenix Controls corporation [35] (Fig. 1). Although no specific pressure differential is required by the BMBL, a common differential used in BSL 3 laboratories and which should be applied to wards within the same context is approximately 0.05 WC (12.45 Pa). However, some biosafety manuals, such as the 3rd edition of the Laboratory Biosafety Guidelines (Health Canada, Ottawa), recommend a differential of ±25 Pa [3].

In this particular setting, the access for a patient into the HLIU should be different from that of HCWs and other patients. A BSL 4 ward is a BSL 3 ward built separately from other patients' facilities, for which the air filtration should be double HEPA filtered. A double door pass through autoclave is mandatory. All entering employees must completely change clothing, and before leaving they should shower before putting their street clothing on [45,49]. All effluents should be decontaminated. A framework for the design and operation of an HLIU has been recently released by the European Network of Infectious Diseases [7]. Negative-pressure plastic isolators for patients with dangerous infections have been envisaged since the early 1980s. The 'isolator system' was set up in an attempt to treat patients with suspected haemorrhagic fever [43] and some are still in use (see Fusco *et al.* in this issue). Since the SARS epidemic, several other ambulatory concept isolation rooms with HEPA filtration units have become commercially available.

Management of Suspected HID Patients

Respiratory hygiene and the 'cough etiquette'

Based on studies of SARS transmission, it appears that measures designed to control respiratory droplets and secretions, along with hand hygiene, would offer significant protection for other patients and HCWs who have close contact with source patients [10,40]. Given the challenge of recognizing early cases of HID, and considering the potential spread of respiratory infections in healthcare settings, a broader strategy to prevent healthcare-associated transmission of respiratory illnesses has been suggested. The CDC healthcare facility guidelines describe a new approach to managing patients with febrile respiratory illness, which has been termed 'respiratory hygiene/cough etiquette'. Patients with cough and fever should be encouraged to report symptoms at admission [10]. Patients with fever and cough should be asked to separate themselves from other patients in the waiting area, to wear a surgical mask, and to disinfect their

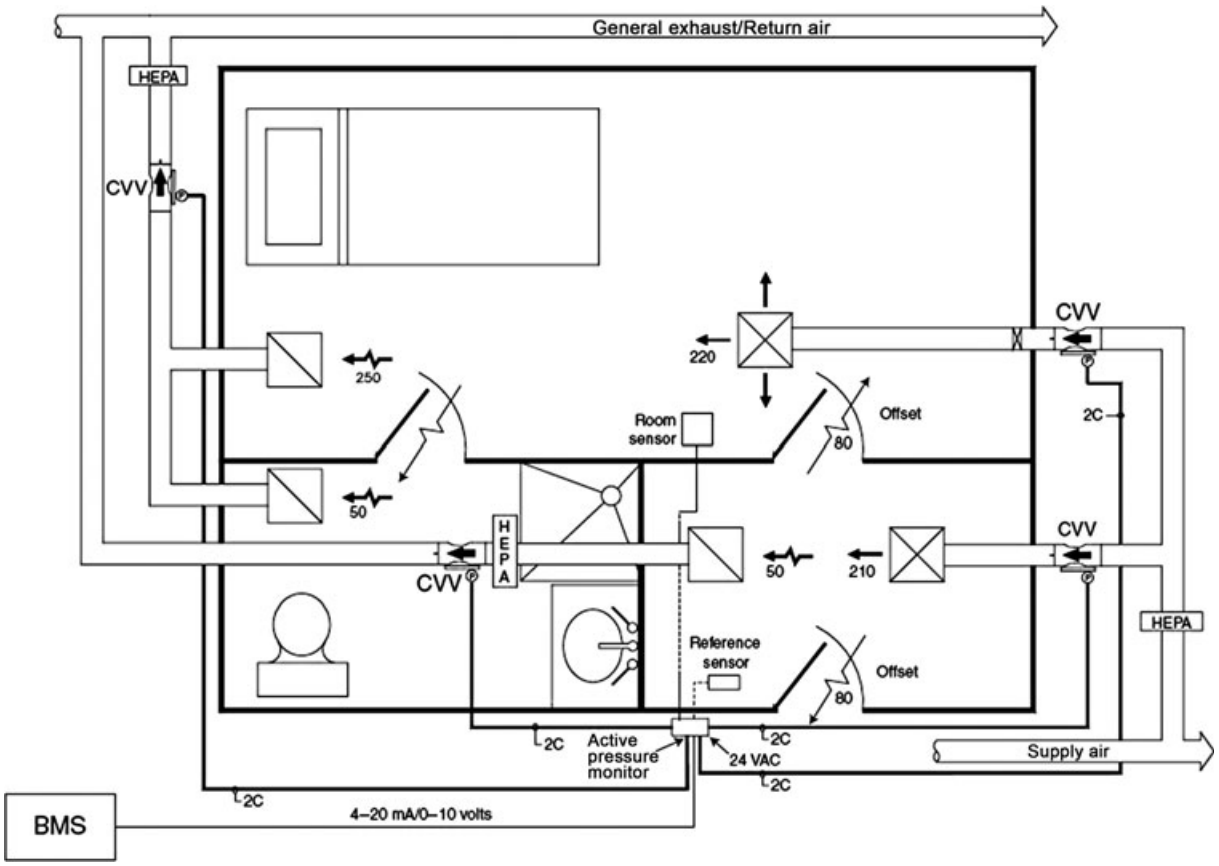

FIG. 1. Example of an airborne isolation room with protective environment (anteroom positive pressure to corridor) as described in reference [35].

hands. Signs concerning 'etiquette' should be posted in the waiting areas to promote these measures and educate both the patients and the HCWs. These patients should be examined and evaluated as soon as possible by the emergency staff in a single room. The emergency staff should wear at least FFP1 or 2 (N95) personal protective mask, gown and gloves. Chest X-ray should be performed separately from other patients by HWCs wearing mask and gloves as described above. When pneumonia is diagnosed upon chest X-ray, a systematic examination of sputum for Alcohol addiction resistant should be undertaken. The transfer of a patient to the infectious diseases ward or other ward should be done by an employee protected with a mask, and the patient should be isolated in a single room with droplet precaution; this isolation must be maintained until the diagnosis is established.

There are three situations in which a patient would need to be admitted into an HLIU. The first involves a patient returning from abroad where an epidemic due to a yet-unknown contagious agent, or due to known class 3 or 4 agents such as SARS CoV, is ongoing. In this context, international surveillance of emerging infectious diseases and outbreaks is mandatory, and is being organized in Europe and throughout the world. Epidemic intelligence encompasses all activities related to early identification of potential health hazards to further establish a risk assessment (see Arias Bohigas *et al.* in this issue). The second situation involves a laboratory worker contaminated during duty in a registered BL 3 or 4 laboratory [27,39], and the third involves a single patient or several patients who have been contaminated by intentionally released class 3 or 4 agents (i.e. bioterrorism). It is likely that if an outbreak of human-to-human transmissible disease begins in one country, that country may miss the first case. This emphasizes the importance of routine respiratory and hand hygiene in the healthcare setting, and of mandatory surveillance of healthcare personnel [29].

Admission to the emergency department

In most instances, a patient suspected to be infected with a highly contagious agent, such as SARS Co-V, would be referred to the emergency department (ED) of a general hospital until a suitable network for the care of such patients is effectively established at a national level. Thus, the EDs of all hospitals should be prepared for such an event, and both training and an infrastructure should be available [29]. These patients are usually referred by general practitioners for a suspected HID. If they correspond to the case definition

they should be directly placed in an HLIU or in isolation rooms (IR) of the ED, if available, until a firm diagnosis is made and the suspected HID is ruled out. During admission to the ED, the patient should avoid any contact with other patients and unprotected HCWs, meaning that direct access from outside to the IR or the HLIU is necessary [42]. IRs in the ED should be at least BSL 2 level, preferably upgraded to BSL 3, with an independent negative pressure air system if possible (Fig. 1). While general respiratory hygiene rules ('cough etiquette') apply to every ED of each general hospital, IRs or HLIUs might apply to referral hospitals, only as HID patients are referred. A patient with a possible or confirmed HID, if not admitted directly to a HLIU, should be transferred from the IR of the ED to the HLIU in a secured manner by using, if possible, safe isolator transportation systems [17] (see Schilling *et al.* in this issue) .

Diagnosis laboratory

To reduce the risk of transmission to HCWs, patient sampling should be done in the IR at the ED or directly in the HLIU, depending on the availability of facilities. It is important to remember that the first aetiology of fever in a traveller from a tropical region is malaria and that this diagnosis is far more likely than that of an emerging HID. All diagnostic tests should be carried out, if possible, in a BSL 3/4 laboratory, including routine haematology and clinical chemistry as well as blood film for malaria. The BSL 3/4 diagnostic laboratory should be located as near as possible to the HLIU, to avoid unnecessary transportation [7]. Even if the use of an auto-analyser might be safe for sample analysis, handling of a sample suspected to be highly contagious, such as Ebola virus-contaminated blood, cannot be done safely in a routine laboratory. An alternative is that routine testing is done in the HLIU at the patient's bedside. Consequently, related research and the development of bedside or point-of-care diagnostic testing models are mandatory. This is one of the objectives of the European network of BSL 3/4 laboratories, which develops, standardizes and organizes quality assurance exercises for new diagnostic assays (see Ippolito *et al.* in this issue).

Hospitalization in the HLIU

Among the existing HLIUs, some are revertible (i.e. BSL 3 wards that are routinely used as infectious diseases wards but which can be rapidly converted to a BSL 3 ward); others are dedicated to such situations (see Fusco *et al.* in this issue) (Fig. 2). The number of HLIUs required per country has been suggested to be a number sufficient to allow transportation of specimens or patients within 6 h [7]. The HLIU should preferably be located alongside a tertiary (specialist referral) hospital. It would, preferably, be a stand-alone structure [7] with engineering and operational protocols appropriate for positioning within a multi-storey building. The current philosophy of the HLIU is that infection control should take precedence over all other aspects of care, and that care of HID patients should be provided in the HLIU only (see Fusco *et al.* in this issue). Radiography should be provided at bedside to avoid transportation of the patient [11,14], and interpreted using a picture archiving communication system if available [42,44]. An ultrasound sonographic scanner should be specifically designed and kept in the HLIU. The transducer should be covered with disposable covers for all patients. The examination should be kept as short as possible, only as necessary to determine the clinical situation. Because computed tomography scan or magnetic resonance imaging is sometimes mandatory for the patient's survival, preparations should be made to reconfigure the radiology department into low- and high-risk areas, to reprogramme examination, and to identify specific transportation of patients from the HLIU, using isolation carriers as necessary. It is strongly recommended to train radiology personnel in infection control measures.

Paediatric patients

Nosocomial infection has been identified as a major problem in paediatric wards and compliance with isolation procedures has to be ensured [13,36]. During the SARS epidemic, the stringent infection control measures inevitably conflicted with the usual family-centred nursing practices [21]. However, for infection control reasons, in cases of HID, family interaction should be minimized and all children suspected of having HIDs should be hospitalized in an HLIU. For this reason, HLIUs should be equipped to care for children and the paediatric staff must be specifically trained in infection control.

Intensive care

The risk of being infected with SARS CoV among physicians and nurses who performed or assisted in endotracheal intubation in the ICU has been reported to be approximately 13 times higher than that among those who did not [15]. This might be explained by the fact that patients admitted to ICUs are usually severely ill, coinciding with a high viral load and maximum infectiousness [34]. ICU personnel are consequently exposed to highly pathogenic agents and it is always prudent to limit opportunities for HCW exposure and to perform aerosol-generating procedures in an airborne isolation environment. Meticulous infection control measures are mandatory in the care of such patients. For this reason, caution should be taken to ensure that ICU rooms are maintained with a negative pressure and a minimum of 15 air changes per hour as recommended by the WHO [49].

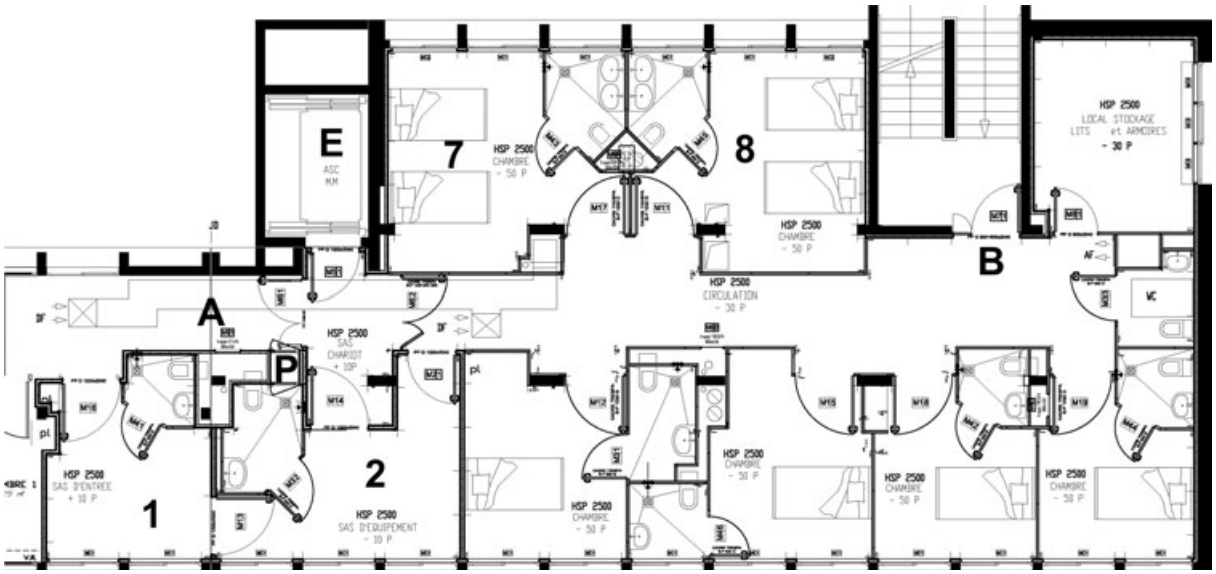

FIG. 2. Example of a revertible highly infectious disease isolation unit. Blueprint of the Bio Safety Level 3 ward of the infectious disease service of Marseille, France showing the unit when working at bio security level 3. Patients occupying the unit are transferred to the main building. Doors A and B are securely closed. The complete unit is under negative pressure (as indicated) with 25 vol./h air change. Beds in rooms 1 and 2 are removed and rooms 1 and 2 are equipped as dressing/undressing and working anteroom, respectively. Rooms 7 and 8 are equipped for intensive care. The dedicated elevator (E) is used for highly infectious disease patient entrance and exit. All effluents are turned to chlorine disinfection. A negative pressure serving hatch (P) is used to enter healthcare material. Blue Print From AP-HM.

The ventilation of IRs is mandatory in the ICU and usually both negative and positive air pressure are available [31]. Although positive air pressure and HEPA filtration of the incoming airflow are mandatory for the protection of immunocompromised patients, in settings such as HIDUs the airflow pressure should be negative and the airflow exhaust through HEPA filter should be as recommended for BSL 3 IRs. The European Network for Infectious Diseases recommends that the care of HID patients who require intensive care should take place in the HLIU if possible [8]. This suggests that HLIUs should be pre-equipped to receive intensive care support. Moreover, the ICU personnel, as the paediatric personnel, should be appropriately trained in infection control in this special setting (eee Bannister *et al.* in this issue). HCWs are particularly exposed to high-risk procedures such as bag-mask ventilation, non-invasive ventilation, endotracheal intubation, actual or potential circuit disconnections, suctioning, tracheotomy and bronchoscopy, with or without bronchoalveolar lavage. Recommendations for infection control in patients with HID during special procedures will be discussed elsewhere [8].

The literature concerning HID, notably SARS, indicates that there is a need for hospitals to be prepared for this possibility and that HID isolation units urgently need to be built in European member state hospitals. The care of HID patients involves stringent infection control measures and regular training of personnel. The articles presented in this theme section of *Clinical Microbiology and Infection* review the knowledge and current European practices in the care of HID patients.

Transparency Declaration

The author declares no conflict of interest with respect to this article.

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