

Clinical Management of Highly Infectious Diseases: a EUNID consensus guideline

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Abstract: A highly infectious disease (HID) is transmissible from person to person; causes life threatening illness and present a serious hazard in health care setting, and in the community, requiring specific control measures. Due to environmental factors, changes in the style of life and many other unknown factors, emergence of such HID is becoming more and more likely. As already demonstrated during the SARS outbreak, health care facilities are likely to be focal points in the future HID outbreaks should they occur. Preparedness planning will be essential for helping facilities manage future outbreaks of emerging or resurgent infectious diseases. Several guidance have been since developed by national and international institutions. To avoid healthcare workers contamination, healthcare of HID patients should follow the same infection control rules than those applied to laboratory workers exposed to similar agents. We review here in the current knowledge and suggest guidelines to optimize the clinical management of highly infectious diseases.

INTRODUCTION

The European Network for Infectious Diseases (EUNID) is a project funded through the European Union whose aim is to identify the current facilities for the clinical management of patients with hazardous infections (Highly Infectious Diseases) and further to define the appropriated specification (Highly Infectious Diseases Isolation Unit : HIDIU) for high level isolation facilities in today's Europe. As a part of this aim we altogether review the literature on highly contagious infectious diseases and we reported the author's experience in managing the contagion. When no literature was available on a specific question or when author's conclusions were not consensually accepted by our group, we specifically debated the question and reported here in our expert consensus. Guidelines were ranked by using the Infectious Diseases Society of America United States Public Health Service Grading System for ranking recommendations in clinical guidelines (**Table 1**)¹. Literature review was made by using Medline® search with the following key words: "SARS (all)", "laboratory-acquired infection", "laboratory-associated infection", "imported (each agent's name)", "each Class 3 and 4 agent's name". More than 1400 references were obtained. Selection criteria within the topic were first the impact factor and half life of the journal, and the availability of journals. Only English and French language articles were reviewed. Internet ® web site such as WHO, CDC and other scientific and international research societies were also used.

1. HISTORICAL BACKGROUND AND OBJECTIVES

1.1. Laboratory accident, worker contamination and outbreaks from laboratory leakage

Among class 3 and 4 agent, laboratory-associated infections have been reported with epidemic typhus², Q fever³, Herpes B virus simiae⁴ tularaemia² pulmonary

plague⁵, Lassa fever⁶, RMSF⁷, Hantaan virus^{8,9}, murine typhus¹⁰, tick borne encephalitis virus TBEV¹¹, sabia virus¹², melioidosis¹³, West Nile virus^{14,15}, and vaccine¹⁶. More recently SARS Co-Virus was laboratory acquired¹⁷ raising worries on bio safety¹⁸. Experience shows that the recognition and isolation of a new infectious agent is often followed by a report of a laboratory-acquired infection caused by the new isolate¹⁹ as reported in SARS¹⁷. Although laboratories that handled class 3 and 4 agents should comply with bio safety regulations, laboratory leakage might happen any time when working with a known agent but also when attempting to isolate an unknown infectious agent such as mimivirus²⁰. 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 happen with SARS Cov¹⁷.

1.2. Travel and imported highly contagious diseases

Travel across the world in few hours as become increasingly frequent. This led to a new epidemiological situation where the risk of worldwide spread of contagion is more and more present. Imported HID such as Lassa fever^{21,22}, and other haemorrhagic fever virus have been reported many time in the literature but have seldom be at the origin of an outbreak except for SARS. This has been the main lesson from the SARS epidemic²³.

1.3. Bioterrorism

Terrorist attacks using biologic agents pose a substantial threat to the safety, health and security of country 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 effect²⁴. These consequences would likely have been exponentially greater if the terrorists had utilized an agent that cause a

communicable disease because this could have resulted in the rapid spread of secondary infection ²⁴ .

2. HID and HIDIU

A highly infectious disease (HID) is transmissible from person to person; causes life threatening illness and present a serious hazard in health care setting and in the community, requiring specific control measures. Agents responsible for these diseases are class 3 and 4 agents as define by the CDC in the 4th edition of the BMBL manual ²⁵ . Considering the fact that in some situation such as caught, the inoculum spread by the patient to which the personnel is exposed is likely to be equivalent as that received by a laboratory worker during specimens handling, health care of such patient should be performed in BSL 3 or 4 level wards to ensure the same level of protection and security to health care worker than to laboratory worker exposed to the same agent. A highly infectious disease isolation unit (HIDIU) also called Biocontainment Patient Care Unit (BPCU) ²⁶ is an Airborne Infectious Isolation ward with the same bio safety level as that defines for laboratory (**Figure 1**). Situations that indicate the use of such highly infectious disease isolation unit (HIDIU) 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 or effective antimicrobial therapy . Risk group classification of infectious agent for laboratory practice ^{27,25} , evidence based human to human transmission and author's recommendations for minimum isolation level of patient in health care setting are summarized in **Table 2**.

3. DEFINITION OF THE BIO SECURITY LEVEL

3.1. Bio safety level criteria

3.1.1.1. Laboratory

Levels of bio security have been first defined for laboratory upon the assessed risk of transmission to human and the possible threat (**Table 3**). Infectious agent classified Class 2 need to be worked in Bio Safety Level (BSL) 2, as do Class 3 in BSL 3 and class 4 in BSL 4 laboratories. To assess this level of bio security, guidelines have been drawn by the CDC in the 4th edition of the Biosafety in Microbiological and Biomedical laboratories (BMBL) manual ²⁵ and by the WHO in the 2nd edition of the Laboratory Safety manual ²⁸ and are briefly summarized in **Table 4** ²⁹.

3.1.1.2. Isolation room and ward

A BSL 3 ward is define as a ward full filling the chart of BSL3 level laboratory ^{25 28}. Briefly it is a negative pressure ward with an anteroom and single bed rooms. The air is HEPA filtered and exhausted outside, the intake is HEPA filtered, the number of air changes is at least 12/hour (depending on each state law) and depressurisation is monitored by an audible and visual device as recommended by the American Institute of Architects ³⁰ and the AIHA ³¹ and described in the Health Care facility design resource manual published by the Phoenix Controls corporation ³². Although no specific pressure differential is required by the BMBL a common differential used in BSL3 laboratories and that should be applied to ward with the same setting is approximately 0.05 WC (12.45 Pa) , but some bio safety manual as the 3rd edition of the Health Canada's laboratory bio safety guidelines ³³ recommend a differential of +/- 25 Pa. All effluents should be decontaminated. In this particular setting the access for patient to the HIDIU should be different than that of health care workers and from other patients. A BSL4 ward is a BSL3 ward built separately from other patients facilities for with the air filtration should be double HEPA filtered. A double door pass through autoclave is mandatory. On entering personnel must put on a complete

change of clothing and before leaving , they should shower before putting on their street clothing^{28 25} . HID isolation rooms should be at least BSL2 level with an independent negative pressure air system as described in the Health Care Facility Design Resource Manual³² **(Figure 2)**

3.1.1.3. Other isolation facilities

Negative-pressure plastic isolator for patients with dangerous infection has been imagined since early 80's. The "Isolator system" was set up in attempt to treat patient with suspected hemorrhagic fever³⁴ . Since SARS epidemic several other ambulatory concept isolation room with HEPA filtration unit have been commercially available.

4. PREVENTION OF HUMAN TO HUMAN TRANSMISSION OF HID

4.1. Prevention of hospital acquired HID in health care setting

Given the challenge of recognizing early cases of HID and considering the potential for spread of respiratory infections in healthcare settings, contributors to the CDC SARS guidance recommended a broader strategy to prevent healthcare-associated transmission of respiratory illnesses. 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 to other patients and HCWs who have close contact with source-patients^{35,36} . Beyond HID , these measures would also help prevent the transmission of many other important pathogens that are spread by the droplet route, such as influenza and *Mycoplasma pneumoniae*³⁷ . The CDC healthcare facility guidance describes a new approach to managing patients with febrile respiratory illness, which has been termed "**respiratory hygiene/cough etiquette.**"

5. MANAGEMENT OF SUSPECTED HID PATIENTS

5.1. Situations in which a patient would need to be admitted in HIDIU

Among the several situations that may be imagined, ongoing epidemics abroad of a yet unknown contagious agent or a known Class 3 or 4 agents such as SARS-CoV, or viral hemorrhagic fever is the most likely. Another situation is that of a laboratory worker that became sick after been exposed to known agent in a registered BL3 or 4 laboratories during his duty such as the last SARS outbreak in Singapore³⁸ or in China³⁹. The third situation is that of intentionally released of Class 3 or 4 agents (bioterrorism). Nevertheless it is likely that if an outbreak of human to human transmissible disease begins in one country, that country would probably miss the first case. This underlines the fact that other implementations such as routine respiratory and hand hygiene in health care setting, and health care personnel surveillance are mandatory⁴⁰.

5.2. Admission to Emergency Department

Because they were facing an unknown HID and they were not prepared Emergency Department (ED) of general hospitals paid an heavy tribute to HID notably SARS^{41,42,43,44}. Since then most of our hospital are not yet prepared to face this situation⁴⁵. In most instances patient suspected to be infected with a highly contagious agent such as SARS Co-V, would be addressed to the ED of general hospitals by their general practitioner until suitable network for care of such patients will be effective in each country. As a consequence EDs of any hospitals should be prepared for such event and both training and structure should be offered to them⁴⁰ (All).

5.2.1. Routine protection: Respiratory hygiene and the "Cough Etiquette"

Patient with cough and fever should be encouraged to report symptoms at admission^{37,46}. At presentation, patient with fever and cough should be proposed to wear a surgical mask and to disinfect their hand, to wait separately from other patient in the

waiting area, to be examined and evaluated as soon as possible by the emergency staff in a single room ⁴⁶. “Etiquette” (signs) should be posted in the waiting areas to promote these measures and educate patients and HCW staff. The emergency staff should wear at least FFP1 or 2 (N95) personal protective mask, gown and gloves (All). Chest-X ray should be performed separately from other patient by HWC wearing mask and gloves as cited above. Transfer of patient to the infectious diseases or other ward should be done by mask protected personal and the patient should be isolated in a single room with droplet precaution and isolation maintained until diagnostic ruled out ⁴⁷ (All).

5.2.2. Isolation of suspected IHD patients

These patients are most of time addressed by general practitioners for suspected HID. If they respond to case definition they should be directly placed in HIDIU or in HID isolation rooms of the emergency department, if available, to be ruled out. During admission the patient should avoid any contact with other patient and unprotected HCW meaning that a direct access from outside to the HID isolation rooms is necessary ⁴⁸ . HID isolation rooms of the emergency department should be at least BSL2 level complemented with an independent negative pressure air system (BIII) preferably upgraded to BSL3 if possible . While general respiratory hygiene rules (“cough etiquette”) apply to every ED of every general hospital, HID isolation rooms or HIDIU might applied to referral hospital only as usually HID patient are announced (BIII). A patient with as possible or confirmed HID, if not admitted directly to HIDIU, should be transferred from the HI isolation room of the ED to the HIDIU in a secured manner by using if possible safe isolator transportation systems ⁴⁹ (BIII).

5.3. Diagnosis laboratory

To reduce the risk of transmission to HCW patients' sampling should be done in the isolation room at the emergency department or in the HIDIU depending on availability. All diagnostic test should be carried if possible in a BSL3/4 laboratory^{25,28} including routine haematology and clinical chemistry as well as blood film for malaria (All) . It is here important to remember that the first aetiology of fever in tropical traveller is malaria and that this diagnosis is far more likely than a new emerging HID. Even if auto-analyser might be safe for sample analysis, handling of sample suspected to be highly contagious such as Ebola virus contaminated blood cannot be done safely in routine laboratory. An alternative if that routine test be done in the HIDIU at patient's bedside. The BSL3/4 diagnostic laboratory should be located as near as possible from the HIDIU to avoid unnecessary transportation.

5.4. Hospitalisation in HIDIU

The number of HIDIU has been suggested to be at least of two per European member state allowing maintenance and repair when needed (BIII). The HIDIU should be preferably located alongside a tertiary (specialist referral) hospital. It would preferably be a stand-alone pavilion⁵⁰ but with appropriated engineering and operational protocols be positioned within a multi-storey building (BIII) . The current philosophy of HIDIU is that infection control should take precedence over all other aspect and that health care of HID should be provided in HIDIU only.

5.4.1. Paediatric patient

During SARS epidemic infection control overshadowed the family-centred nursing practices in the management of paediatric patients⁵¹. The stringent infection control measures inevitably conflicted with the usual family-centred nursing practices⁵². In case of HID family participation should be minimized (All). Children are not little adults, nosocomial infection was identified as a major problem in paediatric wards

and compliance with isolation procedures had to be ensured^{53,54}. For infection control reason all children suspected with HID should be hospitalized in HIDIU but all effort should be made to be prepared and to be able to provide nursing care as close as possible to Bowlby and Robertson philosophy⁵².

5.4.2. Intensive care

The risk of being infected with SARS-Cov among physician and nurses who performed or assisted in endotracheal intubation in ICU was about 13 times higher than among those who did not⁵⁵. This might be explained by the fact that patients admitted in ICU are usually severely ill coinciding with high viral load and maximum infectiousness⁵⁶. Nurses who became ill were often exposed to SARS-CoV within 48 hours of admission while the patient usually deteriorated with symptoms increasing the spread of droplets or aerosols (dyspnoea, cough...) ^{57,58}.

Non invasive ventilation (NIV) is a standard mode of ventilation assist in early acute respiratory failure and ARDS due to various causes. While mortality benefit was not shown, NIV could reduce intubation rate and thus the complication associated with intubation and mechanical ventilation. Despite concern about potential aerosol generation, NIV has been reported to be effective in the treatment of SARS-related ARF without posing infection risk to HCWs^{59,60,61,62}. Consequently intubation could be avoided in up to two-third of the cases in some studies^{63,64}. To reduce aerosol generation exhalation ports that generate round-the-tube airflow are preferred to those producing jet outflow⁶⁵.

To avoid endotracheal intubation, mechanical ventilation should be reserved for patients who failed NIV or who are contraindicated (uncooperative, disturbed consciousness, high aspiration risk hemodynamic instability...) (BII). This recommendation has been found inapplicable by our intensive care expert who

stated that those patients are usually seen late and clinically unstable needing mechanical ventilation primarily.

The duration of manual ventilation during resuscitation procedures should be reduced to a minimum. Endotracheal intubation should be performed by the most skilled person available ⁶⁶ using rapid sequence induction: risk of aerosol generation is lowest when the patient is paralysed.

To limit HCW exposure it is recommended to perform aerosol generating procedures in an airborne isolation environment. Caution should be taken to ensure that ICU rooms were maintained with a negative pressure and a minimum of 15 air changes per hour as recommended by WHO ⁶⁸. Ventilation of isolation room is mandatory in ICU and most often both negative air pressure and positive air pressure are available ⁶⁹. Although positive air pressure and HEPA filtration of entering airflow is mandatory for immune-compromised patient protection, in a setting of environmental protection such as in highly infectious diseases the airflow pressure should be turned negative and the airflow exhaust through HEPA filter as recommended in BSL 3 level isolation rooms. The used of powered air purifying respiratory (PAPR) might be useful in giving a supplementary protection especially during high risk manipulation such as endotracheal intubation ^{65,70} (CIII). Our experts report misuse and leakage by PAPR dysfunction in their practice and we think that the use of complete personal protective equipment with appropriate gloves, gown, and mask in a negative pressure environment is more secure (BIII).

5.4.3. Special procedures

Due to the risk of the transmission to HWC, managing invasive diagnostic or therapeutic procedures in patient with HID is a challenge. However there are few reports on hospital acquire HID during invasive procedure before the SARS era. This

is likely to be related to the fact that outbreak of HID had until now only occurred in countries or in time where such techniques were not available. SARS epidemic brings a new highlight of the risk in such situation as it was an incredibly contagious disease⁷¹. However it is important to notice that available evidence on risk factors is weak and somewhat indirect according to the commonly accepted hierarchy of evidence. A great deal of work needs to be carried out to separate the essential risk factors from the superfluous ones.

5.4.3.1. Bronchoscopy

Although in some situation (ongoing outbreak of a known disease) diagnostic bronchoscopy or flexible lung endoscopy is not necessary, some situation needs such invasive procedure to rule out differential diagnosis or to collect sample for laboratory investigation if the etiological agent is not known. Transmission of SARS have been reported or suggested after intubations of patients⁷¹ and in HWC that used a nebulizer in patient with SARS⁷² resulting in a major outbreak. In a retrospective study among critical care nurses in Toronto the probability of a SARS infection was of 6% of nurses who assist during intubation suctioning and manipulating the oxygen mask. In the same study wearing a mask especially a N95 was protective⁷³. It has also been suggested that high flow rate oxygen mask may results in health care worker infection⁷¹. Bronchoscopy as well as been suggested to increased SAS-CoV transmission in HCW⁶¹. Aerosolisation of lung pathogens during flexible endoscopy is well documented and hospital acquired infection is well documented during these procedures leading to standard guidelines for flexible endoscopy⁷⁴. It is likely that similar transmission would happen with other respiratory agent such as avian influenza, Hantaan (Sin nombre virus) pulmonary syndrome and others. Bronchoscopy, airway suctioning and other types of procedure that may

induce coughing and may expose HCW to potentially infected aerosolized respiratory droplets pose an increased risk of transmission of those agents.

As a consequence, facing with HID especially with respiratory transmission needs to first avoid unnecessary procedures, second to comply with established guidelines for prevention of respiratory infection during such procedure and third to performed these procedures in an air-controlled environment. In most hospital, rooms dedicated for bronchoscopy are under negative pressure but as recommended these are not necessary air filtered³⁰. In the case of HID we recommend either to perform the bronchoscopy in the HIDIU at the bed side avoiding unnecessary moving of the patient or if not possible to perform it in an appropriated room of at least BSL2 (All).

5.4.3.2. gastroscopy

In addition to respiratory transmission, SARS-CoV may also be transmitted by direct contact with infected respiratory secretions and other body fluids such as do hemorrhagic fever viruses^{75,76,42,77}. Indirect contact with contaminated environmental surfaces and inanimate objects (fomites) is suspected to have resulted in the transmission of SAR-CoV, as suggested by reports that health care workers who had no direct contact with SARS infected patients became infected^{78,79,80,75,42}. Data suggest that SASR-CoV such as orthopoxvirus and others can survive on hard surfaces such as plastic and stainless steel, for several hours, if not days^{42,80,81}. Moreover many class 3 and 4 viruses as well as SARS-CoV have been identified in human faeces^{79,76,80,42}. Although there is no published report of transmission of SARS during GI endoscopy, the potential exists for the transmission of such agents to HCW and other patient during GI endoscopy⁸². Here again GI endoscopy should be avoided in HID patient unless they are absolutory necessary. Adherence to current guidelines for reprocessing of endoscopes also is

recommended for prevention of transmission Class 3 and 4 viruses via both potentially contaminated GI endoscopes and bronchoscopes⁸² (All). Single, disposable endoscopic accessories and devices are an alternative to sterilization of reusable devices; proper disposal of these devices also is essential (CIII).

5.4.3.3. Radio imaging ; CT scan and RMI, Chest X rays and Ultrasound

Most of our knowledge on the management of infection control in radiology department comes from the SARS experience and from tuberculosis. In a recently published study on the exposure of HCW to tuberculosis, radiology technician had a relative risk of positive tuberculin skin test of 1.7 compared to other HCW, and those working for less than 1 year had a lower risk for infection indicating that radiology technician are exposed to TB during their practice⁸³. At the Prince of Wales Hospital in Hong Kong on march 2003 at least 50 HCW were affected by SARS including radiographers⁸⁴. Because imaging plays a role important in the diagnosis and the management of HID the role of the radiology department is to provide an immediate and efficient radiologic service for patient with suspected or confirmed HID. Chest radiography is mandatory in such situation. To minimise the risk of cross-infection to other personnel and to protect other non infected patient transportation of HID patient should be as limited as possible. For ambulatory patients with suspected HID, in order to confirm or to reject the diagnosis, satellite radiography centre should be set up with portable radiography machines, chest stands and lead screens in the vicinity of the emergency rooms dedicated to HID patients⁸⁵ (All). For patient hospitalised in the HIDIU bedside radiography should be provided to avoid transportation of patient^{86,84} (All). Radiograph should be interpreted only by designated radiologist aware of infection control and interpretation throughout a picture archiving and communication system (PACS) should be used if available^{87 84}. The film processing area where

cassettes are brought back to the department after bedside radiography in HIDIU should be considered at high risk unless the cassette were processed in the HIDIU following a protocol of double bag selling and should be disinfected^{86,85}. For ultrasound scanning sonographic scanner as portable radiograph should be designed to be used only for HID patients (AII). One machine should be designed for a specific area such as for HIDIU. The examination should be kept as short as possible to answer the clinical question. The transducer should be covered with disposable covers for all patients (CIII). The value of CT scan in assessing the diagnosis of HID such as SARS has been established and CT scan is sometime mandatory for patient's evaluation⁸⁸ Because this examination can be performed only in the radiologic department, stringent infection control measures need to be followed and this examination performed only if absolutely necessary for patient recovery. It is strongly recommended that the department appoint a staff member to monitor and ensure that all department staff fully complies with the infection control measures according to guidelines (AII). Designated sessions or hours, either outside office hours or at the end of a session, should be assigned for such patients.

Transportation of patient should be carried out in special isolation carrier⁴⁹ or be done through a define way avoiding any contact with other patient or unprotected personnel⁸⁷. The department should be divided in low and high risk areas (BIII). After CT scan the gantry table and floor should be cleansed and the bed linen should be changed. In all cases radiology technicians, radiologist and other radiology personnel should comply with universal precautions including wearing mask, cap, gown and gloves during direct contact with patient. Finally imaging (Chest X ray and ultrasonography) in patient with HID should be carried out at bedside in HIDIU or in isolation rooms of the emergency department. Because CT scan or RMI is sometime

mandatory for patient survival we should be prepared to reconfigure the radiology department in low and high risk area, reprogramming examination, identifying specific way for patient transportation from the HIDIU to the CT scan or RMI including if using specific isolation carriers. Training the radiology staff to infection control measures is strongly recommended (All).

5.4.3.4. Renal dialysis

The main reported dialysis-associated infections are viral hepatitis. As a consequence guidelines have been edited to prevent nosocomial transmission of these agents to personnel and patients⁸⁹. Using these guidelines there is no hospital acquired reported cases of Hantaan hemorrhagic fever with renal syndrome while between 30 and 50 % of patient needs at least HID that need haemodialysis⁹⁰. Most of our knowledge in the management of HID with renal failure has been acquired during the SARS episode. Compared to other, care of patients undergoing renal dialysis pose several additional infection control issues in the disposal of spent dialysate (both haemodialysis and peritoneal dialysis (PD)) and in the prevention of cross-contamination within the dialysis unit⁹¹. During the SARS episode the dialysis patients were kept in the SARS isolation ward along with the other non dialysis SARS patients. All patients with PD were treated with intermittent PD during hospitalization. The dialysis exchange was done by the ward staff, who wore full protective gear as recommended by the WHO, including waterproof disposable gown, cap, gloves, face shield and N95 face mask⁹¹. Spent PD effluent was decontaminated by 2% hypo chloride solution. Haemodialysis was performed in a room specially equipped in the isolation ward designed for SARS patients by the ward staff, who wore full protective gear as recommended by the WHO, including waterproof disposable gown, cap, gloves, face shield and N95 face mask⁹¹. Designated haemodialysis

machines were used with ordinary tap water supply passing through the filter without reverse osmosis or other water treatment. Spent dialysate was decontaminated as described above and all blood tubing was discarded as infectious waste. As potentially contaminated, unspent dialysate concentrate and sodium bicarbonate cartridge was also discarded as infectious waste. The dialysis machine was disinfected after each haemodialysis session with sodium hypochlorite solution. Patients with HID who require dialysis should be hospitalized in HID unit and treated at bedside with either PD or haemodialysis (All).

5.4.3.5. Post-mortem examination

Although autopsies have been conducted safely on HID in some circumstances, sometimes without prior knowledge of the diagnosis such as Ebola hemorrhagic fever, these agents are transmissible at autopsy and raised the concern of protection of pathologist and the autopsy personnel⁹². Tuberculosis was the first reported in the literature and there is no reason to believe that it would not be the case with MDR or XDR tuberculosis⁹³. Aerosol production have been recognised early in this situation and lead to some precaution⁹⁴. During the first episode of HPS in 1993 the first 5 suspected patient were necropsy without any except the standard precaution while the agent was isolated and classified as a Class 3 agent⁹⁵. Fortunately no transmission occurred in autopsy personnel. During the SARS episode number of autopsy have been performed and although there is no case of transmission several authors raise the concern of bio safety in autopsy rooms^{96,95,92}. Before an autopsy is done on a patient suspected to have died from HID, the possible risks and benefits must be carefully considered⁴⁹. Limited autopsy or post mortem collection of blood and percutaneous liver biopsy material may be appropriate⁹⁷ (All). Several pathologists and we recommend that identical precaution should be given to

laboratory than that for autopsy and consequently, patients who died from an unknown HID or those who died from a known Class 3 or 4 agent should be autopsied only if necessary and in BSL3 or 4 isolation room (AII) (HIDIU)^{49,95,96,98}

6. CONCLUSIONS.

Highly Infectious Disease Isolation Units urgently need to be built in European member state hospitals. In most instances we recommend to performed high risk invasive medical procedure in the protective environment of HIDU (BCPU). Our recommendations are in perfect accordance with that published by the American consensus²⁶. The lack of clinical studies explains that some guidelines reported herein might be sometime found excessive. However, awaiting more collective experience (hopefully never happen) everything should be done to avoid the spread of a highly infectious disease within our countries.

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Table 1 : Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

	Name	Comments	Risk Group *	H-H spread (ref)	Literature based Level of evidence **	Minimum Proposed isolation level in health care setting
Bacteria	<i>Brucella spp</i>		3	none		2
	<i>C burnetii</i>	Pneumonia	3	Yes ^{10,12}		2
	<i>B pseudomallei</i>	Pneumonia	2-3	Unusual	2C	2
	<i>F tularensis</i> type A		3	none		2
	<i>Mycobacterium Bovis</i>	not BCG	3	none		2
	MDR <i>M tuberculosis</i>		3	Yes	1A	3
	<i>Rickettsia Rickettsii</i>		3	none		2
	<i>R conorii</i>		3	none		2
	<i>R akari</i>		3	none		2
	<i>R australis</i>		3	none		2
	<i>R sibirica</i>		3	none		2
	<i>R japonicum</i>		3	none		2
	<i>R typhi</i>		3	none		2
	<i>R prowazekii</i>		3	none		2
	<i>Orientia tsutsugamushi</i>		3	none		2
	<i>Yersinia pestis</i>	pneumonia	3	Yes ¹⁴	1A	3
Viruses	Absettarov , hanzalova,	Central European Tick	3	none		2

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	Hypr, Kumlinge (CETBE)	Borne encephalitis				
	Hantaan viruses	HFSR and other Puumala, Seoul, and Sin nombre viruses	3	Yes ⁴		2
	Hendra and Hendra like virus	Equine morbillivirus encephalitis	3	unknown	3C	2/3
	Herpes virus Simiae (B) virus		3/4	Yes ^{8,14}	2C	2/3
	Influenza Virus ***	Pre-pandemic genotype as for example (H5N1)	Move from 2 to 3 ⁶	yes	2C	2/3
	Lymphocytic choriomeningitis virus	LCM Virus	3	none		2
	Small Pox and other Pox Viruses	Level 2 for vaccine in vaccinated personnel	4	Yes ¹⁴	1A	3/4
	Vesicular Stomatitis virus	Highly contagious by contact	3	unknown	3C	3
	Rift Valley fever virus		3	none		2
	Yellow fever virus	In vaccinated personnel	3	none		2

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	West Nile virus		3	none		2
	Japanese encephalitis virus	In vaccinated personnel	3	none		2
	Chikungunya virus	One suspected HAI by contact	3	Yes ¹¹	2B	2
	Venezuelan equine encephalomyelitis viruses	Everglade Virus type 2 and others	3	none		2
	Lassa fever virus		4	Yes	1A	3/4
	Ebola Virus		4	Yes	1A	3/4
	Guanarito virus	Venezuelan hemorrhagic fever	4	Yes ⁵	1A	3/4
	Congo Crimean Hemorrhagic fever virus		4	Yes ¹⁴	1A	3/4
	Junin virus	Argentine hemorrhagic fever (BSL3 if vaccinated)	3/4	unknown	3C	3/4
	Kyasanur Forest disease		4	unknown	3C	3/4
	Marburg		4	Yes	1A	3/4
	Omsk hemorrhagic		4	unknown	3C	3/4

	fever					
	Russian spring summer encephalitis	TBE group	4	unknown		3/4
	Lassa fever		4			
	Machupo virus	Bolivian hemorrhagic fever	4	Yes ⁵	1A	3/4
	Sabia	Brazilian hemorrhagic fever	4	unknown	3C	3/4
Giant Viruses	Mimivirus	Hospital acquired Pneumonia ^{2,9,13}	3****	unknown		2
Fungi	<i>Histoplasma capsulatum</i>	Histoplasmosis	3	none		2

- *As define by in ref ^{3,7} and by the European Economic Community (Directive 93/88/EEC, Oct 93)**
- ** Category 1A : reported in human with isolation of the agent , Category 2B reported with serological evidence or other indirect evidence, 3C likely to occur in certain situation but insufficient data to support the assumption
- *** Bio safety level for influenza virus is currently BSL2 but this level has been update to BLS3 for pre-pandemic viruses like HPAI viruses ⁶
- **** Bio safety level not officially attributed but authors recommend BSL3 level as laboratory acquired pneumonia has already occurred ¹³

Table 1 : Risk group Classification of infectious agent for laboratory practice, evidence based human to human transmission and minimum proposed isolation level of patient in health care setting ^{1,3} . It is important to notice that most of those guidelines are based upon a very small number of clinical cases.

Table 2: Risk Group and Bio-safety Level Definitions

[European Economic Community \(DIRECTIVE 93/88/EEC, Oct, 1993\)](#)

- (1) Group 1 biological agent means one that is unlikely to cause human disease;
- (2) Group 2 biological agent means one that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available;
- (3) Group 3 biological agent means one that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available;
- (4) Group 4 biological agent means one that causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.

[CDC/NIH Biosafety in Microbiological and Biomedical Laboratories \(4th Edition 1999\)](#)

- (1) BIOSAFETY 1 is suitable for work involving well-characterized agents not known to cause disease in healthy adult humans, and of minimal potential hazard to laboratory personnel and the environment.
 - (2) BIOSAFETY LEVEL 2 is similar to Level 1 and is suitable for work involving agents of moderate potential hazard to personnel and the environment.
 - (3) BIOSAFETY LEVEL 3 is applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents which may cause serious or potentially lethal disease as a result of exposure by the inhalation route.
 - (4) BIOSAFETY LEVEL 4 is required for work with dangerous and exotic agents which pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease.
-

Table 3: Summarized guidelines for BSL 2/3 and 4 laboratories (Ref 26)

Biosafety measures	biosafety levels		
	P2	P3	P4
Laboratory design			
1. laboratory identification ('biological hazard' sign)	yes	yes	yes
2. laboratory separated from other premises at least by a door	yes	yes	yes
3. access to the laboratory via an airlock	no	optional (yes if negative pressure)	yes
4. controlled and lockable access access possible for authorized personnel only	yes	yes	yes by an airlock
5. facility for hermetically closing the laboratory for disinfection (fumigation)	optional	yes	yes
6. air filtration through a laboratory (HEPA filter) with evacuation of air to the exterior	no	yes	yes (double HEPA filter)
7. filtration of air entering the laboratory	no	optional	yes
8. presence of an observation window or equivalent system enabling the occupants to be seen	optional	yes	yes
9. means of communication with the exterior	no	optional	yes
10. laboratory maintained at negative pressure relative to neighboring facilities	no	yes	yes
11. alarm system to detect any unacceptable change in air pressure	no	yes if negative pressure	yes
12. emergency electrical energy supply	no	optional	yes
13. emergency ventilation system	no	no	yes
Laboratory resources			
1. microbiological safety station	yes	yes	yes (type III)
2. protective clothing	yes	yes ^A	yes ^B
3. facility for storing protective clothing in the laboratory or unit	yes	yes	yes
4. shower for decontamination of workers	no	optional	yes
5. hand washing: wash-basins with faucets that can be operated without using the hands. Eye-washing stations	yes	yes	yes
6. surfaces resistant to water, easy cleaning without areas inaccessible to cleaning	yes ^C	yes ^D	yes ^E
7. surface of benches impermeable to water and resistant to acids, alkalis, solvents and disinfectants	yes	yes	yes
8. effective control of vectors such as rodents and insects	yes	yes	yes
9. presence of an autoclave	yes ^F	yes ^G	yes ^H
10. presence in the laboratory of basic equipment (labeled equipment)	no	yes	yes
operating procedures			
1. storage of biological agents in a secure facility	yes	yes	yes (restricted access)
2. handling of infected materials and contaminated animals in an appropriate biosafety system	optional	yes	yes
3. use of specific containers for contaminated needles and soiled, pointed or cutting objects	yes	yes	yes
operating procedures			
4. minimization of aerosol formation	yes	yes	yes
5. control of aerosols	minimization	prevention	prevention
6. gloves	optional	yes	yes
7. inactivation of contaminated equipment and wastes	yes	yes	yes
8. decontamination of laboratory equipment	yes	yes	yes
9. sterilization/disinfection of wastes from sinks and showers	no	yes	yes

^A : appropriate protective clothing and overshoes

^B : complete clothing change before laboratory entry/exit

^C : floors

^D : floors, walls and ceilings

^E : walls, ceilings and floors resistant to chemical cleaning agents

^F : readily accessible and, if possible, in the building

^G : in the laboratory, double entry, or in immediate proximity, with evaluated appropriate procedures enabling transfer to an autoclave outside the laboratory conferring the same protection and with the same implementation control

^H : in the laboratory, double entry

Figure 1 : Blue print of the HIDIU : BSL 3 ward of the Infectious disease and tropical services in Marseille France. Upper Right the isolated Infectious disease building connected with main part of the hospital.

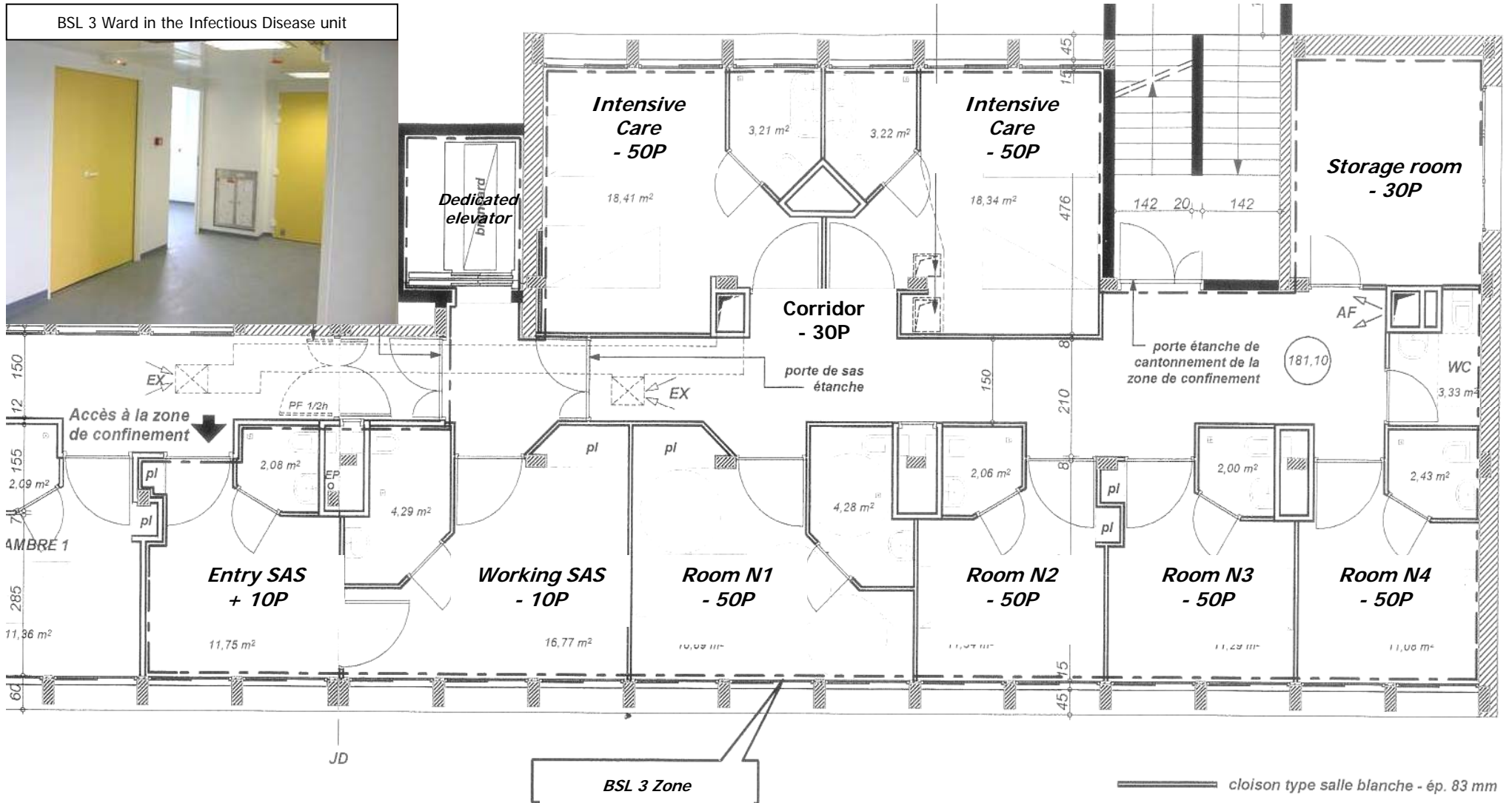


Figure 2 : An example of what could be a BSL2 room as described in the healthcare design facility resource from the Phoenix Controls corporations available at <http://www.phoenixcontrols.com/solutions.html>

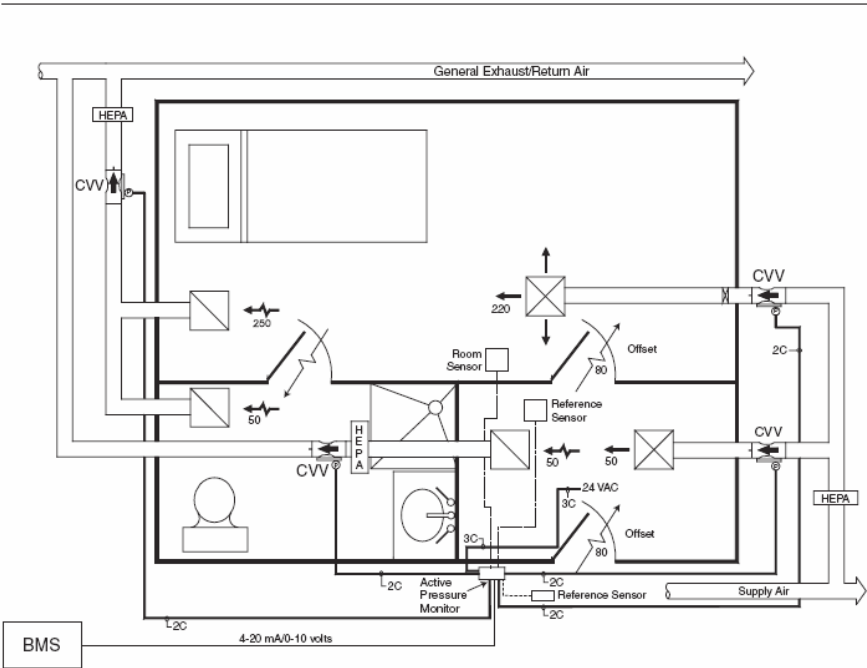


Figure 3-3. An example of an infectious isolation environment with an anteroom negative to the corridor.

LEGEND	
⊕	Factory Installed Pressure Switch
CVV	Constant Volume Valve
BMS	Building Management System
—	Field Installed Pneumatics
— _{XC}	Cable by Others
⊗	Reheat Valve

- NOTES:
1. Refer to Room Schedule Sheet (RSS).
 2. Valves are shown horizontally for diagrammatical purposes only. Actual valve orientation must be specified for each application.
 3. Depending on the form of isolation, ventilation design or jurisdiction, HEPA filtration may or may not be required.
 4. In this example, the anteroom is positive to the patient room and negative to the corridor.
 5. Valves in the anteroom are used for maintaining ventilation and proper pressurization in lieu of balancing dampers.

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