



Lessons Acquired from HCV Outbreaks in Hemodialysis Units

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DISCLOSURES

- Honoraria, consulting fees from MSD, Astellas, Boehringer Ingelheim, Novartis
- Direct and indirect ownership of stock in pharma and biotech companies, hospitals, and clinics as part of retirement portfolio

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Outbreaks in Asia

- Difficult to pull any reported events in literature
- Crude survey of Malaysia, Thailand, Taiwan contacts – no reports
- Report in literature = Japan
- Singapore in last few years in Renal patient ward

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HCV OUTBREAK IN AN ACUTE HOSPITAL RENAL UNIT

- Between April and September 2015, 22 cases of acute HCV infection was identified amongst patients admitted to Ward 64A or Ward 67 at SGH
- Screening of those who had been admitted to these wards from January to September 2015 identified three more cases, giving a total of 25 cases
- 20 were renal transplant cases
- There were eight deaths within the cluster

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HCV INFECTION

- Renal Ward was originally operating in Ward 64A, moved to Ward 67 on 6 April 2015 when Ward 64A was under renovation, and back to Ward 64A on 28 August 2015
- Laboratory analysis by SGH (and subsequently confirmed by A*STAR) noted the presence of a strain of HCV, of genotype 1b, among cases
- Thus an outbreak involving a common strain of HCV was established

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Independent Review Committee

- Track 1:

- Appointed two teams of international experts from the United States' Centers for Disease Control (US CDC) and Prevention and Johns Hopkins University to strengthen its capabilities and to provide additional technical and scientific input to the committee's review

- Track 2:

- Appointed three Resource Persons – Professor Tan Chorh Chuan, President of NUS, Professor Chee Yam Cheng, Senior Advisor to National Healthcare Group, and Mr Ong Pang Thye, Deputy Managing Partner, KPMG to evaluate the various parties' responses to the incident
- Included reviewing MOH's role in the outbreak, IRC member Dr Jeffery Cutter (Director, Communicable Diseases Division, Ministry of Health) recused himself

Four hypotheses were tested

- Drug diversion
- Intentional harm
- Product contamination
- Breaches in infection control

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IRC findings

- Susceptible cases comprising mainly immunocompromised kidney transplant patients and the introduction of HCV (probably by the patient identified as the earliest infected case) led to acute infections with extremely high quantities of virus in these patients.
- Affected patients had many exposures to intravenous medications and/or laboratory tests that required blood taking, exacerbating the risks of HCV spread through gaps in infection control practices
- Gaps in infection control practices (processes involving intravenous procedures), environmental cleaning, and prevention of environmental contamination. These potentially facilitated HCV transmission in the two affected wards.
- These could have been accentuated by the shift to another ward where the layout was different from the ward that staff were familiar with

Recommendations

- To minimise the risk of infection transmission:
- Review standard operating procedures and practices on infection control, with a view to reduce risk of environmental contamination, and to ensure adequate environmental cleaning and disinfection
- Adhere to standard precautions for infection control, as laid out in US CDC guidelines
- Strengthen the framework for supervision and monitoring of staff to ensure compliance with standard operating procedures

Key actions and responses on 5 items

- (a) recognition of an infectious disease outbreak
- (b) notifications to MOH
- (c) outbreak management and containment
- (d) communications and escalation
- (e) roles and responsibilities of key players during the outbreak.
- Surveillance system works well for community outbreaks of known infectious diseases and hospitals have robust frameworks to handle common Healthcare-Associated Infections (HAIs), the HCV outbreak highlighted a gap

Recognition

- The Renal Unit did not recognise the outbreak in a timely manner and there was a delay in reporting to Infection Control for help in containment

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Notifications

- MOH was not notified by doctors and laboratories of all the cases in the cluster
- MOH-CDD did not classify the initial communicable diseases notifications as acute HCV infections despite some cases having abnormal liver function tests, as the cases were assessed not to meet the case definition of an acute infection at the time

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Outbreak management and containment

- Started investigations into the HCV cluster from mid-May 2015, and enhanced infection control measures from early-June, investigations performed were incomplete
- Several elements of outbreak investigation such as assessing the severity and extent of the outbreak were done after meeting with the Director of Medical Services (DMS) on 3 September, such as appointing an external party to chair Medical Review Committee to determine if there were related deaths due to the HCV infection and setting up a Quality Assurance Committee to do a root cause analysis

Communications and escalation

- Within the hospital, communication with senior management took place early
- However, in the absence of an established framework for the unusual and unfamiliar event of the HCV outbreak, there was a delay in escalation from the hospital to MOH
- In addition, within MOH, there was no single division with clear responsibility and capability to deal with the issue, resulting in a gap in ownership, until the matter was escalated to the DMS

Roles and responsibilities

- Within the hospital, there did not appear to be clear roles and responsibilities for the management of unusual hospital outbreaks
- Within MOH, the DMS assessed on 3 September 2015 that more information was needed to determine the severity and extent of the outbreak, and requested the hospital to complete key pieces of work within two weeks
- The Minister was therefore only informed of the issue on 18 September, and briefed on 25 September, after the hospital submitted their investigation report on 24 September

Conclusions

- Unusual outbreak of a blood-borne infection with low prevalence rates in Singapore was likely due to a combination of multiple overlapping factors concentrated during the period of April to June 2015 in the Renal Wards
- In particular, the concentration of very ill patients and gaps in infection control practices provided an environment for the infection to spread
- While existing surveillance and response systems lend themselves well to known community outbreaks and HAIs, the system response to the incident, which is considered an unusual one, revealed some gaps in the system
- Recommended improving the notification and surveillance system for acute HCV; designating a single team within MOH to oversee surveillance, investigation and management of outbreaks and ensure adequate expertise to facilitate outbreak investigation; and strengthening escalation processes for HAIs and unusual risks

Key practical problems

- Acute hospital surveillance
- No standard reporting and data collection within hospital
- Changing medical teams and inability to identify trends

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Annex 1. New dialysis screening protocols for Blood Borne Diseases at renal dialysis centres**

Pre-Dialysis status	Before admission	3 monthly [2 - 4 monthly] [†]	6 monthly
All patients	Anti-HBs, HBsAg, Anti-HBc (Total) [‡] , ALT, Anti-HCV HIV Ag-AB	ALT	
a) <u>HBV-susceptible</u> [i.e. i) HBsAg, anti-HBs and anti-HBc (total) negative; or ii) HBsAg, anti-HBs negative, and anti-HBc (total) positive and HBV DNA negative]		HBsAg & anti-HBs	
b) <u>HBV-immune</u> (anti-HBs pos. [≥10 mIU/mL] and HBsAg, anti-HBc negative; anti-HBc positive and anti-HBs > 100)			
Anti-HCV negative		Anti-HCV [‡]	
Anti-HIV negative			HIV Ag-AB

^{*} 2 - 4 monthly depending on operational requirements

[†] Only patients tested positive for Anti-HBc (Total) before admission should be screened for HBV DNA to rule out occult HBV infection

^{**} Patients tested positive for Anti-HCV, HBsAg and Anti-HIV or routine dialysis screenings should be referred to an appropriate clinician for further assessment and evaluation.

[‡] Patients tested positive for Anti-HCV, should be tested with EIA supplementary tests or HCV RNA to confirm Hepatitis C infection. Patients who repeatedly test positive for Anti-HCV but negative for the supplementary tests, can be considered for direct HCV RNA testing.

Singapore MOH guidelines 2019

Reported HCV outbreaks

- Considered papers published between 1992 and 2015
- 5 parameters
 - Total number of cases
 - Duration of the outbreak (number of months between the day of onset and the day of end of the outbreak or as reported by the authors)
 - Attack rate (AR) (number of cases/number of susceptible individuals)
 - Fatality rate (FR) (number of deaths/number of cases)
 - Time to publication
- Considered as molecular epidemiology techniques only the analysis of infection cluster(s) through PCR of 1 or more selected region(s) of the viral genome
- Standard epidemiology included serological analysis, genotyping, or sub-typing

TABLE I - Synopsis of reviewed outbreaks (1992-2007): epidemiology

Authors	Country	Publication year	Outbreak duration (mo)	Incident HCV, <i>n</i>
Allander T, et al	Sweden	1994	16	5
De Lamballerie X, et al Olmer M, et al	France	1996	12	2
McLaughlin K, et al	UK	1997	4	4
Le Pogam S, et al	France	1998	8	4
Mizuno M, et al	Japan	1998	18	2
Irish D, et al	UK	1999	2	1
Izopet J, et al	France	1999	12	11
Katsoulidou A, et al	Greece	1999	6	5
Grethe S, et al	Germany	2000	9	14
Abacioglu Y, et al	Turkey	2000	19	3
Hosokawa N, et al Iwasaki Y, et al	Japan	2000	20	5
Delarocque-Astagneau E, et al	France	2002	42	9
Kokubo S, et al	Japan	2002	2	11
Halfon P, et al	France	2002	22	2
Ansaldi F, et al	Italy	2003	12	12
Furusyo N, et al	Japan	2004	2	5
Sartor C, et al	France	2004	2	1
Bracho M, et al	Spain	2005	44	3
Savey A, et al	France	2005	9	22
Kondili L, et al	Italy	2006	4	4
Hmaied F, et al	Tunisia	2006	2	1
Hmaied F, et al	Tunisia	2007	2	1

NA = information not available; mo = months.

TABLE II - Synopsis of reviewed outbreaks (2008-2015): epidemiology

Authors	Country	Publication year	Outbreak duration (mo)	Incident HCV, <i>n</i>
Spada E, et al	Italy	2008	7	4
Girou E, et al	France	2008	9	2
CDC	US (NY)	2009	82	9
Thongsawat S, et al	Thailand	2008	36	51
Lampe E, et al	Brazil	2008	14	8
CDC	US (IL)	2010	NA	11
CDC	US (OH)	2010	NA	5
CDC	US (WI)	2010	NA	3
CDC	US (VA)	2010	NA	7
CDC	US (MD)	2010	NA	7
Almroth G, et al	Sweden	2010	2	1
Lanini S, et al	Italy	2010	3	13
CDC	US (PA)	2013	NA	18
CDC	US (CA)	2013	NA	4
CDC	US (GA)	2013	NA	6
CDC	US (TX)	2013	NA	2
CDC	US (MD)	2013	NA	8
CDC	US (NJ)	2013	NA	21
Szucs M, et al	Hungary	2014	7	17
CDC	US (WA)	2014	NA	3
CDC	US (TN)	2014	NA	2
CDC	US (NJ)	2014	NA	4
CDC	US (NJ)	2014	NA	2

NA = information not available; mo = months.

TABLE III - Synopsis of reviewed outbreaks (1992-2007): pathways of spread of HCV

Authors	Risk factor	Lapse considered responsible for transmission
Allander T, et al	Sharing the same dialysis shift (and room) with HCV-infected patients	Not identified
De Lamballerie X, et al Olmer M, et al	Sharing the same dialysis room with HCV-infected patients	Failure to follow precautions in emergency
McLaughlin K, et al	Sharing the same dialysis shift with HCV positive patients	Failure to perform universal precautions; Patient-to-patient transmission by close proximity
Le Pogam S, et al	Sharing the same dialysis machine with HCV-infected patients	No sterilization procedure after dialysis with HCV-infected pts Poor glove use in emergency situations
Mizuno M, et al	Patients treated during the same shift shared by HCV positive patients	Inappropriate practices of a staff member common to patients
Irish D, et al	Dialysis on the same shift with HCV-infected patients	Not identified
Izopet J, et al	Dialysis on the same area and during the same shift or on the previous one	Contamination of surfaces and instruments by HCV particularly during busy periods or in emergency
Katsoulidou A, et al	Dialysis on the same shift with HCV infected patients	Failure to change gloves between patients
Grethe S, et al	NA	Not identified
Abacioglu Y, et al	Dialysis on the same day, during the same shift (sometimes using the same machine) with HCV infected patients	Failure to change gloves in emergency; Lack of environmental decontamination between HD sessions
Hosokawa N, et al Iwasaki Y, et al	Dialysis at the station adjacent to that of patient with chronic HCV infection	Inappropriate glove use
Delarocque-Astagneau E, et al	HD sessions following HCV-infected pts on the same machine; HD sessions with HCV-infected patients in the same room; HD sessions adjacent to HCV-infected patients; Injections through HD machine	Failure to change gloves; Inadequate environmental control; Poor hand washing for HCW between tasks and procedures or patients; Blood contamination of the pressure-sensing port of the HD machine
Kokubo S, et al	NA	Heparin saline solution contaminated from HCV
Halfon P, et al	NA	Not identified
Ansaldi T, et al	Sharing the same dialysis shift (different or same room) with HCV infected patients	Not identified
Furusyo N, et al	NA	Heparin-saline solution ampoule contaminated from HCV
Santor C, et al	Sharing the same dialysis machine with HCV-infected patients	Contamination of the venous pressure monitoring system
Bracho M, et al	Not reported	Not identified
Savay A, et al	Connection by a nurse who had connected an HCV-infected patients just before	Horizontal transmission (via health care workers); Vertical transmission (dialysis machine); or both Accidental flooding of pt blood into the external filters of the arterial pressure tubing set
Kondil L, et al	Sharing the same dialysis shift with HCV-infected patients	Contaminated multidose vials
Hmaïed F, et al	Sharing the same dialysis shift (different area) with HCV-infected patients	Poor glove use; Undersluffing
Hmaïed F, et al	Sharing the same dialysis shift (and area) with HCV infected patients	Sharing articles between pts and/or via nurses and medical staff

CDC = Centers for Disease Control and Prevention.

TABLE IV - Synopsis of reviewed outbreaks (2008-2015): pathways of spread of HCV

Authors	Risk factors	Lapse considered responsible for transmission
Spada F, et al	Sharing the same dialysis shift with HCV-infected patients	Vertical transmission (by contaminated dialysis machines); Horizontal transmission (by health care workers and/or environmental contamination)
Girou E, et al	Sharing the same dialysis shift with HCV-infected patients	Low nurse-to-patient ratio; Low compliance to hand hygiene
CDC (NY)	NA	Failure to change gloves and perform hand hygiene between patients; Breaches in environmental cleaning and disinfection practices
Thongsawat S, et al	NA	Failure in adherence to universal precautions; Insensitivity of serologic screening
Lampe E, et al	Sharing the same dialysis room (or the same day) with HCV positive patients	Not identified
CDC US (IL)	NA	Preparation of injections in a contaminated environment; Failure to separate clean and contaminated areas; Failure to change gloves and perform hand hygiene between tasks or patients
CDC US (OH)	Dialysis on same machine immediately after HCV positive patients	Preparation of multiple intravenous medication at the dialysis station; Failure to routinely clean dialysis machine or dialysis station surface between patients; Use of a mobile medication or supply cart that was moved between dialysis stations
CDC US (WI)	Dialysis at the station adjacent to that of patients with chronic HCV	Use of mobile carts to transport supplies or medications to patients
CDC US (VA)	Dialysis at the station adjacent to that of patients with chronic HCV; Receipt of intravenous medications from vial used for more than 1 patient;	Failure to routinely clean dialysis machine or dialysis station surfaces between patients; Use of mobile cart to transport supplies or medications to pts;
CDC US (MD)	Dialysis during the shift to lowering that of HCV-infected pt (but not the same machine) Dialysis on same machine immediately after HCV-infected patients	Administration of intravenous medications from a single-dose vial to multiple patients Preparation of multiple intravenous medication at the dialysis station; Failure to routinely clean dialysis machine or dialysis station surface between patients
Albroth G, et al	Sharing the same dialysis shift with HCV-infected patients	Not identified
Lanini S, et al	Undergoing HD on MWF pm shift	Contaminated multidose vial containing heparin
CDC US (PA)	NA	Multiple lapses including hand hygiene, glove use, vascular access care, medication preparation, cleaning and disinfection
CDC US (CA)	NA	Not identified
CDC US (GA)	NA	Failure to maintain separation between clean and contaminated work spaces
CDC US (TX)	NA	Not identified
CDC US (MD)	NA	Breaches in medication preparation and administration practices; Breaches in environmental cleaning and disinfection
CDC US (NJ)	NA	Breaches in medication preparation and administration practices; Breaches in environmental cleaning and disinfection
Szucs M, et al	NA	Sharing vials containing heparin or saline solution
CDC (WA)	NA	Poor glove use and hand hygiene; Breaches in environmental cleaning and disinfection practices
CDC (TN)	NA	Breaches in environmental cleaning and disinfection practices
CDC (NJ)	NA	Poor washing hand before/after glove use; Poor cleaning dialysis chairs/areas surrounding the station
CDC (NJ)	NA	No separation between clean and contaminated areas; Poor disinfection of clamps; Poor cleaning/dialysis chairs/priming bucket; Poor cleaning/disinfection of HD access site

CDC = Centers for Disease Control and Prevention.



Summary of findings from Tables

- A definite patient-to-patient transmission pathway was not recorded in a number of outbreaks (n = 11, 24%)
- Internal contamination of machine was mentioned or suspected as a source (n = 8, 18%)
- Epidemiological investigations coupled with the application of molecular techniques in many outbreaks (n = 31; 69%)
- Sharing of contaminated multidose vials (heparin or saline solution) was the suspected lapse considered (n = 6; 13%)
- The most frequent transmission pathway was multiple deficiencies in applying standard procedures or dialysis specific precautions (n = 29; 64%)

Contaminated dialysis and space

- Data supporting transmission of HCV by HD machines are controversial
- Findings suggest that this route is uncommon and plays a minor transmission role
- In the absence of visible blood, HCV RNA was found on the external surfaces of the dialysate (inlet-outlet) connector of a dialysis machine and on a waste cart
- Blood contamination has been seen on environmental surfaces and equipment but also on items and surfaces outside the treatment area

Patient-care practices

- After adjusting for nondialysis-related HCV risk factors, patient-care practices independently associated with higher prevalence of HCV infection included
 - reusing priming receptacles without disinfection (OR, 2.3, 95% CI, 1.4; 3.9)
 - handling blood specimens adjacent to medications and clean supplies (OR, 2.2; 95% CI, 1.3; 3.6)
 - using mobile carts to deliver injectables (OR, 1.7; 95% CI, 1.0-2.8)

Shimokura G, Chai F, Weber DJ, Samsa GP, Xia GL, Nainan OV, Tobler LH, Busch MP, Alter MJ. Patient-care practices associated with an increased prevalence of hepatitis C virus infection among chronic hemodialysis patients. *Infect Control Hosp Epidemiol*. 2011 May;32(5):415-24

Summary

- Many reports suggest that an exact mode of patient-to-patient transmission of HCV in the HD setting could not be ascertained
- The putative mechanism of patient-to patient transmission was mostly unsatisfactory compliance to standard/specific infection prevention practices
- Full adherence to control procedures against the diffusion of HCV within dialysis units and appropriate screening for anti-HCV antibody are encouraged

KIDGO 2018 guidelines

- >50% of health care–associated HCV outbreaks from 2008 to 2015 reported to the CDC occurred in hemodialysis settings

Table 3 | Factors and lapses in infection control practices associated with transmission of HCV infection in dialysis units

- Preparation of injections in a contaminated environment (including at patient treatment station)
 - Reuse of single-dose medication vial for more than 1 patient
 - Use of mobile cart to transport supplies or medications to patients
 - Inadequate cleaning or disinfection of shared environmental surfaces between patients
 - Failure to separate clean and contaminated areas
 - Failure to change gloves and perform hand hygiene between tasks or patients
 - Hurried change-over processes
 - Low staff-to-patient ratio
-

Box 1 | Summary of KDIGO HCV Recommendations

CHAPTER 3: PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

3.1: We recommend that hemodialysis facilities adhere to standard infection control procedures, including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (see Table 1) (1A).

Table 1 | Infection control practices (“hygienic precautions”) particularly relevant for preventing HCV transmission

-
- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
 - Proper injectable medication preparation practices following aseptic techniques and in an appropriate clean area, and proper injectable medication administration practice
 - Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
 - Adequate separation of clean supplies from contaminated materials and equipment
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3.1.1: We recommend regular observational audits of infection control procedures in hemodialysis units (1C).

3.1.2: We recommend *not* using dedicated dialysis machines for HCV-infected patients (1D).

3.1.3: We suggest *not* isolating HCV-infected hemodialysis patients (2C).

3.1.4: We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (2D).

3.2: We recommend hemodialysis centers examine and track all HCV test results to identify new cases of HCV infections in their patients (1B).

3.2.1: We recommend that aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related (1A).

3.3: Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients (*Not Graded*).

Table 6 | Strategies to support adherence to infection control recommendations in hemodialysis centers

- It is important for the designers of dialysis units to create an environment that makes infection control procedures easy to implement. Adequate hand-washing facilities must be provided, and the machines and shared space should make it easy for staff to visualize individual treatment stations. Certain jurisdictions specify the area around a hemodialysis machine.
- The unit should ensure that there is sufficient time between shifts for effective decontamination of the exterior of the machine and other shared surfaces.
- The unit should locate supplies of gloves at enough strategic points to ensure that staff has no difficulty obtaining gloves in an emergency.
- When selecting new equipment, ease of disinfection should be considered.
- There are indications from the literature that the rate of failure to implement hygienic precautions increases with understaffing. Understaffing has been associated with hepatitis C outbreaks. Certain jurisdictions specify a specific nurse-to-patient ratio (e.g., 1:4 in France). Formal health care training of all staff should be required (e.g., in the US, technicians provide most direct hemodialysis care but lack standardized training). Dialysis units that are changing staff-to-patient ratios, or introducing a cohort of new staff, should review the implications on infection control procedures and educational requirements.
- Resource problems should be handled by carrying out a risk assessment and developing local procedures. For example, if blood is suspected to have penetrated the pressure-monitoring system of a machine but the unit has no on-site technical support and no spare machines, an extra transducer protector can be inserted between the blood line and the contaminated system so that the dialysis can continue until a technician can attend to the problem.

The following are useful CDC and WHO informational resources to improve hand hygiene, environmental cleaning and disinfection, and injection safety:

http://www.cdc.gov/dialysis/PDFs/collaborative/Env_notes_Feb13.pdf

http://www.cdc.gov/dialysis/PDFs/collaborative/Env_checklist-508.pdf

<http://www.cdc.gov/dialysis/PDFs/dialysis-Station-Disinfect-Tool-508.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-Hand-Hygiene-Observations.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Checklist.pdf>

<http://www.cdc.gov/dialysis/PDFs/collaborative/Hemodialysis-InjectionSafety-Observations.pdf>

http://www.who.int/gpsc/5may/hh_guide.pdf (See Figure 9 of document and pp. 44–49)

CDC, Centers for Disease Control and Prevention; US, United States; WHO, World Health Organization.

A few notes

- Isolation not recommended
 - Not much evidence, only 1 RCT
 - Isolate room, patient, machine, staff ?
- Control measures are effective
- Treatment of HCV (reduce active prevalence, reduce incidence)
- Audits and use of surveillance data
 - Any new HCV positivity in HD patients = HD associated infection until proven otherwise
- Screening of all patients before dialysis placement, and routine surveillance
- Infrastructure/space
 - Physical separation of patients, medication preparation areas, etc.

Answering my brief

- Examples from Asia
- Better infrastructure design
- Better auditing measures
- Better system design (lower patient/staff ratio)
- Better staff training/education
- Attitude when facing seroconversions in HD

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