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Clinical practice guidelines for the provision of renal service in Hong Kong: Infection Control in Renal Service

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A GENERAL INFECTION CONTROL MEASURES IN RENAL UNITS

A1 Design of the renal unit

The increased risk of exposure to blood, body fluids and other potentially infectious materials during dialysis procedures and the immunocompromised state of the patients with end-stage kidney disease are unique features of the Renal Units which predispose to nosocomial infections, especially blood borne infections, among patients and staff. The design of the Renal Units should take such infection risks into consideration and facilitate the implementation of a high level of infection control measures to minimize the risk of nosocomial infections in the Renal Units.

Guideline statements

1. There should be adequate operating space in the Renal Units, between beds and haemodialysis (HD) stations for staff to safely carry out their clinical duties.[1] [D]

2. The lighting, temperature and noise levels of the Renal Units should be optimized to provide a comfortable working environment for staff.[1] [D]
3. There should be designated single-patient rooms or cubicles in the Renal Units to isolate patients with potentially infectious diseases. [R]
4. There should be designated patient rooms or cubicles in the Renal Units to cohort patients infected with the same strain of multidrug-resistant microorganisms. [D]
5. There should be designated clean areas in the Renal Units for the preparation, handling and storage of medications, equipment and supplies.[2] [R]
6. There should be designated areas in the Renal Units for handling or storing contaminated or used supplies and equipment, which are separated from areas where medications, clean equipment and supplies are handled or stored.[2] [R]
7. There should be designated areas, which are separated from the clinical areas, for staff to eat and drink.[3] [R]
8. There should be adequate hand hygiene facilities such as hand wash basins or alcohol-based hand rub dispensers in the Renal Units, which are easily accessible to staff, patients and visitors. [R]
9. There should be adequate supplies of personal protective equipment in the Renal Units, which are readily available at the point of use. [R]
10. There should be dedicated HD machines for patients who are hepatitis B virus (HBV) infected.[4] [R]
11. There should be designated segregation areas for HBV-infected patients to undergo HD.[4] [R]

A2 Hand hygiene

Hand hygiene refers to either hand washing with soap and water or application of an alcohol-based hand rub. It has been well documented that contaminated hands of health-care workers play an important role in the transmission of health-care-associated infections.[5] Hand hygiene is regarded as the most important measure in reducing the transmission of health-care-associated infections in the health-care settings. Adherence to proper hand hygiene practice is of paramount importance in preventing cross infection in the Renal Units.

Guideline statements

1. Staff working in Renal Units should cover cuts or abrasions on their bodies, especially the exposed parts, with waterproof dressings.[6] [R]
2. Staff must perform hand hygiene (i) before touching a patient; (ii) before a procedure; (iii) after a procedure or exposure to body fluids; (iv) after touching a patient and (v) after touching a patient's surroundings.[7] [R]
3. When the hands are visibly dirty or visibly soiled with blood or other body fluids, the hands should be washed with soap and water and dried thoroughly with paper towel.[7] [R]
4. When the hands are not visibly soiled, routine hand hygiene can be carried out with alcohol-based hand rubs.[7] [R]
5. Hand hygiene facilities should be near the site of patient care such as the HD station.[8] [R]
6. There should be adequate number of hand wash basins in the Renal Units to allow easy access for the staff to perform hand hygiene.[8] [R]
7. There should be at least one hand wash basin in each segregation area of dialysis.[1] [R]
8. Alcohol-based hand rub should be made readily available in the Renal Units and be placed at the point of patient care such as next to each HD station or at the end of each patient's bed. [R]
9. All patients and visitors should carry out hand hygiene on entering and leaving the Renal Units.[9] [R]
10. All patients should clean their hands with alcohol-based hand rub before taking meals and medications, and practice hand hygiene after using bedpan, urinal and attending toilet. [R]

A3 Personal protective equipment

The clothing and body parts of staff working in the Renal Units may become contaminated with blood, body fluids, multiresistant microorganisms or other potentially infectious materials during patient care practices. Such contaminations may serve as a source of cross infection among staff and patients. Personal protective equipment refers to specialized clothing or equipment such as gloves, protective gowns, aprons, masks, goggles and face shields worn by a health-care worker that serve to prevent them from getting in touch with infectious materials. Appropriate use of personal protective equipment will help to protect the staff from acquiring infections and minimize the risk of cross infection between patients.

Guideline statements

1. There should be sufficient supplies of personal protective equipment, which are of different sizes to suit the needs of staff, in the Renal Units and at the point of patient care. [R]
2. Staff should wear personal protective equipment including gloves, protective gowns, aprons, masks, goggles and face shields appropriate to the nature of the procedure being performed whenever there is a likelihood of exposure to blood, body fluids and other infectious materials.[1] [R]
3. Staff should change gloves and aprons and perform hand hygiene between caring for different patients and working at different HD stations.[6] [R]

4. Staff should change gloves and aprons and perform hand hygiene between different procedures for the same patient.[6] [R]
5. Staff should change their personal protective equipment as soon as feasible when it becomes contaminated with blood or body fluids.[6] [R]
6. Staff should remove personal protective equipment including gloves, apron and/or gowns and perform hand hygiene after performing a procedure or on leaving the clinical work area. [R]
7. Staff should dispose used or contaminated personal protective equipment in proper waste containers. [R]

A4 Medication safety

Outbreaks of blood borne infections have been reported among HD patients because of improper preparation, handling and administration of parental medications.[10] Examples of unsafe practices that contribute to these outbreaks include contamination of the medication vials with patients' blood or body fluids and reuse of syringe in the administration of the medications between patients. Careful attention to medication safety helps to minimize the risk of inadvertent transmission of infection to patients through the parental routes.

Guideline statements

1. Staff should carry out hand hygiene before and after handling medications. [R]
2. All parental medications should be prepared using aseptic techniques in a designated clean area in the Renal Unit away from the HD stations.[8] [R]
3. Single-use or single-dose medication vials should be used whenever possible. [D]
4. If multiple-dose medication vials have to be used, each vial should be used on a single patient only and should be clearly labelled with the patient's name and for use by that patient only.[1] [D]
5. Multiple-use of bottles or bags of intravenous (IV) fluids should be avoided as far as possible. [D]
6. A new sterile syringe and needle should be used each time medication is aspirated from the medication vial. [R]
7. Single-dose IV fluid containers should be used for IV flush purposes. [D]
8. Medications delivered to the patient's dialysis station should be used for that patient only and should not be used on another patient. Unused medications should be discarded.[6] [R]
9. Trays used to deliver medications to individual patients must be cleaned between uses for different patients.[6] [R]
10. Common medication carts or trolleys should not be used to deliver medications to patients.[6] [R]

A5 Cleaning and disinfection of the environment

The environmental surfaces of the Renal Units such as the floor, dialysis chairs, countertops and the exterior surfaces of HD machines could easily become contaminated with patients' blood or body fluids, making them a potential source of nosocomial infections. Regular cleaning and disinfection of these surfaces will minimize the risk of transmission of infections in the Renal Units.

Guideline statements

1. Supporting staff allocated to work in the Renal Units should receive appropriate training in infection control.[11] [R]
2. Supporting staff should wear appropriate personal protective equipment while carrying out routine cleaning of the Renal Units. [R]
3. The environmental surfaces of the Renal Units and the exterior surfaces of medical equipment should be cleaned and disinfected regularly (at least daily) using 1:99 household bleach (1 part 5.25% sodium hypochlorite solution in 99 parts water) or other equivalent disinfectants.[11] [R]
4. The environmental surfaces of the Renal Units and the exterior surfaces of medical equipment should be cleaned and disinfected using 1:49, 1000 ppm of sodium hypochlorite solution if clostridium difficile or norovirus infection is suspected. [R]
5. The environmental surfaces of the Renal Units should be cleaned and disinfected when they become visibly soiled or after contamination.[8] [R]

A6 Cleaning and disinfection of medical instruments and equipment

Guideline statements

1. Frequently used medical equipment such as tourniquets, blood pressure cuffs and clamps should be designated to each patient. [D]
2. The touched surfaces of reusable medical equipment should be cleaned with detergent and water between patient uses.[12] [D]
3. Equipment that are used at a patient's dialysis station should be dedicated for use by that patient only or thoroughly disinfected prior to return to a clean area for use by another patient.[6] [R]
4. Disposable patient-care items (e.g. blood pressure cuffs) should be used whenever possible when the patient is potentially infectious or when contact precautions are warranted.[8] [D]
5. Non-disposable items that cannot be cleaned and disinfected thoroughly (e.g. cloth-covered blood pressure

cuffs) should be dedicated for use on a single patient.[8] [R]
6. The external surfaces of the dialysis machine should be cleaned with detergent and hot water and dried thoroughly after each patient use in accordance with the manufacturer's instructions, [R]

A7 Sharps disposal

Sharps used in the Renal Units such as dialysis needles may be contaminated with patients' blood or body fluids. Accidental injury of staff working in the Renal Units by used sharps poses a risk of transmission of blood borne infections from patients to staff.

Guideline statements

1. Staff should exercise caution when handling sharps in the Renal Units, especially when they are contaminated with blood or other body fluids, to avoid accidental injuries. [R]
2. Sharp boxes should be made readily available in the Renal Units and should be located as close as possible to the point of use. [R]
3. Staff who has used sharps when carrying out clinical procedures in the Renal Units should be responsible for the prompt and safe disposal of the sharps.[12] [D]
4. Staff must not recap or re-sheath used sharps such as dialysis needles.[1] [R]
5. All sharps should be discarded into an approved sharp box at the point of use. [R]
6. Sharps boxes should be large enough to contain the types of sharp devices that are being used in the Renal Units.[6] [R]
7. Sharps boxes should not be filled with used sharps to more than three quarter full. [R]
8. Sharps containers should be properly sealed and labelled, before being transported to their safe disposal in accordance to code of practice for the management of clinical waste.[13] [R]

A8 Waste management

Substantial amount of clinical waste is generated in the Renal Units during their daily operation. Clinical waste from Renal Units includes any waste contaminated with blood or body fluids or other potentially infectious materials, used peritoneal and HD fluids. Clinical waste should be regarded as potentially infectious and be handled with care to avoid contamination of the environment.

Guideline statements

1. All clinical waste generated from the Renal Units should be placed in specific color-coded containers, properly sealed, packaged and stored temporarily as required.[13] [R]
2. All clinical waste should be collected by licensed clinical waste collectors for its safe disposal in accordance to code of practice for the management of clinical waste.[13] [R]
3. Used peritoneal dialysis (PD) fluids should be disposed of directly to the drain or by pouring carefully into a sluice. [R]
4. Used HD fluids should be disposed of directly to the drain. [R]

A9 Management of blood and body fluid spillage

Spillages of blood, body fluids or other potentially infectious materials may lead to the dissemination of infectious agents within the Renal Unit and should be dealt with promptly.

Guideline statements

1. Staff should be trained in the proper disinfection procedures involved in the handling of spillages of blood and other body fluids. [R]
2. Staff should wear appropriate personal protective equipment when dealing with spillages of blood and other body fluids. [R]
3. For spillage of blood and other potentially infectious substances, the visible matter should be cleaned with disposable absorbent material. [R]
4. The spillage area should be mopped with a cloth or paper towels wetted with one part of house hold bleach (5.25% hypochlorite solution) in four parts of water, and left for 10 min. The area should then be rinsed with water.[11] [R]
5. Small spill of blood can also be removed by applying chlorine-releasing granules or powder directly to the spill, which can then be removed using paper towels or wipes.[11] [D].
6. For spillage of other body fluids such as vomitus or spent peritoneal dialysate, the visible matter should be cleaned with disposable absorbent material. [R]
7. The spillage area should be mopped with a cloth or paper towels with 1 part of household bleach (5.25% hypochlorite solution) in 49 parts of water, and left for 15–30 min. The area should then be rinsed with water.[11] [R]
8. Staff should remove the personal protective equipment and perform hand hygiene after handling the spillage of blood or other body fluids. [R]

A10 Staff training

Guideline statements

1. Staff working in the Renal Units including medical, nursing and supporting staff should receive training in

infection control practices, especially proper hand hygiene techniques and appropriate use of personal protective equipment. [R]
2. All health-care workers should attend infection control refresher training course once every 24 months. [R]

A11 Surveillance and audit

Surveillance of dialysis-related infections in the Renal Units involves systemic collection, analysis and interpretation of data concerning infection-associated events which helps to identify trends and develop improvement measures to reduce infection-associated mortality and morbidity.

Guideline statements

1. Each Renal Unit should develop a surveillance program to monitor, review and evaluate the serological status of its patients for blood borne virus, microbiological screening for multidrug-resistant microorganisms and the quality of water for HD. [R]
2. Each Renal Unit should regularly audit the compliance of its staff to infection control practices such as hand hygiene. [D]

B INFECTION CONTROL MEASURES OF THE DIALYSIS FACILITY/DIALYSIS EQUIPMENT

Haemodialysis patients are exposed to a large volume of water (typically 120–150 L) during each HD treatment session. Bacterial proliferation and bacterial biofilm formation might occur on the inner surfaces of the water distribution piping. Contamination of the water used for HD with bacteria and endotoxins produced by the bacteria might lead to the development of pyrogenic reactions (fever, hypotension, nausea vomiting) in the patients undergoing HD. Proper treatment of the water used for HD and regular disinfection of the water distribution system in the HD unit is essential to keep microbiological contamination of the water used for the preparation of dialysis fluid for HD below acceptable limits.

B1 Water quality

Guideline statements

1. The quality of water used for HD should be tested regularly to confirm the proper functioning of the water treatment system and to ensure that the water quality meets the required standards of purity for HD. [R]
2. The total viable microbial count and the endotoxin concentration in the dialysis water used for routine HD should be less than 100 CFU/mL and less than 0.25 IU/mL, respectively.[14] [R]
3. The total viable microbial count and the endotoxin concentration in the dialysis water used for on-line haemodiafiltration should be less than 0.1 CFU/mL and less than 0.03 IU/mL, respectively.[14] [R]
4. If the total viable microbial count of the dialysis water is more than 50 CFU/mL but less than 100 CFU/mL, corrective measures such as disinfection of the water treatment system and retesting the water quality should be undertaken.[15] [R]
5. The Renal Units should have standard operating procedures in place to regularly sample, monitor and record the quality of dialysis water and dialysis fluid.[15] [R]
6. The total viable microbial count and endotoxin levels should be measured at different points along the water distribution system and at different dialysis stations. [R]
7. The total viable microbial count and endotoxin concentration of the reverse osmosis water and dialysate should be monitored at least once a month.[16] [R]
8. Endotoxin levels in the dialysis water and dialysis fluid should be measured regularly using appropriate method such as the limulus amoebocyte lysate (LAL) test or other equivalent methods.[16] [D]
9. Appropriate culturing method, culture media and incubation parameters, such as incubation on Tryptone Glucose Extract Agar at 20–22 °C, should be used to culture bacteria from the dialysis water and dialysis fluid.[16] [D]
10. Water samples collected from the water distribution system or the dialysis machines should be assayed within 30 min after collection or be stored at 4 °C and assayed within 24 h.[17] [R]

B2 Disinfection of the water treatment/distribution system and HD machines

Guideline statements

1. The water treatment system and the water distribution system should be designed in such a way as to ensure smooth flow of water through the system which will minimize the formation of bacterial biofilms and allow routine disinfection of the system.[18] [R]
2. The water treatment system, water distribution system and HD machines should be disinfected regularly by either internal heat sterilization or chemical sterilization or a combination of both methods in accordance to the manufacturer's recommendations. [R]
3. If chemical sterilization is used, appropriate measures should be in place to test for the residual levels of the chemical disinfectants in the dialysis machines. [R]

C PREVENTION OF DIALYSIS ACCESS-RELATED INFECTION

C1 Haemodialysis

Introduction

Catheters are essential medical device for the provision of temporary and long-term vascular access for HD. Both uncuffed and cuffed tunnelled catheters have been used as vascular access for HD patient. In this context, there is a growing trend to use the latter as a long-term vascular access, especially in elderly patients as well as patients with poor cardiovascular disease or diabetes mellitus.[19] The use of HD catheter is associated with HD catheter-related infections such as exit-site infections, catheter-related bloodstream infections (CRBI) or even infective endocarditis, and such risks are increased with duration of placement.[20] Hence, the prevention of HD catheter-related infection significantly improves outcomes in HD patients.

Guideline statements

C1.1. The internal jugular veins are the preferred sites for HD catheter placement. Insertion into femoral veins, especially for tunnelled cuffed catheters, is not encouraged unless jugular vein cannulation is not possible. (R)

C1.2. Aseptic technique should be employed during insertion, manipulation and connection/disconnection of HD catheter. The exit site of HD catheter should be covered by sterile dressing which should be inspected during each HD session and be replaced if no longer clean or intact. (R)

C1.3. The use of antibiotics lock solution can reduce risk of HD CRBI, but its use should be balanced against the benefits and associated risks and should not replace hygienic standards about catheter handling. (D)

C1.4. Application of topical antimicrobial to exit site of HD catheter is not a routine practice in HD catheters, and should be weighed against the emergence of resistant organisms. (D)

Rationale

Femoral positions are at high risk of infection and bacteremia and hence should be avoided if possible as site of HD catheters.[21,22] Alternative sites include subclavian veins but are associated with increased risk of stenosis.[20] Weighed against risks and benefits, the internal jugular veins remain the preferred sites for HD catheter placement.

Although the evidence regarding the use of disposable face masks and gowns protect against the transmission of staphylococcus and other organisms is not convincing,[23] the use of face masks and gowns is relatively harmless and should be undertaken during HD catheter insertions. The HD catheter exit site should always be covered by sterile dressing as long as the catheter is in-situ. One meta-analysis showed that transparent dressing is associated with higher risk of catheter sepsis and bacteremia when compared with gauze dressings.[24] Inspection of the catheter exit site during each HD session facilitates earlier detection and treatment of exit-site infection, and hence helps prevent CRBI. Moreover, the sterile gauze should be replaced when it becomes wet or unclean.

There is mounting evidence to suggest efficacy of antimicrobial locks. Citrate, alcohol, ethylene diamine and antimicrobials have been tested as antimicrobial lock solution.[25–29] Among these agents, the clinical efficacy of citrate had been established in at least two meta-analyses.[25,26] In this context, low concentration (4%) of citrate is preferred to high concentration (>30%) as spillover of the latter into systemic circulation might lead to abrupt hypocalcaemia and cardiac complications,[30,31] pulmonary embolism and systemic toxicities of antibiotics (e.g. ototoxicity in aminoglycosides).[30,32] Hence, the use of antimicrobial lock should be balanced against the benefits and risks in different clinical contexts.

Previous studies have demonstrated the benefits of topical application of antimicrobials on reduction of HD catheter exit-site infections and associated bloodstream sepsis.[33–35] Mupirocin, MediHoney, polysporin triple ointment (Bacitracin, gramicidin and polymixin B) have been used as topical prophylaxis for HD catheter exit sites.[33,34,36,37] In this context, mupirocin and MediHoney have shown similar clinical efficacy and the latter is associated with a theoretically lower risk of resistance.[36]

Limitations

There is limited data to compare the efficacy and costs of different approach to prevention of catheter-related infections. While there is abundant data on nasal application of mupirocin in PD on reduction of exit-site and tunnel tract infection as well as peritonitis, such evidence in HD catheter remains lacking.

Implementation issues

Adherence to standard precautions and aseptic techniques during the handling of HD catheters can be difficult, especially in HD centres with high patient load and turn-over. The emergence of resistant organisms also remains an important issue in HD catheter-related infections.

Audit items

The compliance to standard precautions and aseptic technique during the handling of HD catheter should be continuously reviewed. The rates of HD catheter exit-site infections and CRBI, as well as the organism identified (including the susceptibility profile) should also be regularly audited. Such data will help review and modify current policy for the prevention of HD catheter-related infections in a dialysis unit.

C2 Peritoneal dialysis

Introduction

PD catheter-related infections (i.e. exit-site and tunnel-tract infection) are major risk factors for peritonitis and hence

prevention of PD catheter-related infections can significantly decrease risk of peritonitis.[38,39]

Guideline statements

C2.1. Proper hand hygiene should be undertaken by patients, helpers and health-care providers during the handling and manipulation of the PD catheter and its exit site. (R)

C2.2. The use of antimicrobials with activity against *S. aureus* as exit-site prophylaxis in PD patients is recommended. (R)

C2.3. Intra-nasal application of mupirocin in PD patients with confirmed nasal carriage of *S. aureus* is recommended. (R)

Rationale

Proper hand hygiene is a crucial measure to reduce PD exit-site infections, and should be undertaken by patients, helpers and health-care providers during routine handling of the PD catheter and its exit site.[40] In this context, 70% alcohol-based hand rub is recommended as the most effective hand-cleansing agent before and after exit-site care.[41] Other alternative include handwashing with antimicrobial-containing (e.g. 4% chlorhexidine) soap.[41] Polished nails increase the risk of bacterial contamination with hands and should be avoided in patients, helpers and health-care providers for PD patients.[41]

Mupirocin has established efficacy as prophylaxis for *S. aureus* exit-site infections.[42–47] The use of intra-nasal mupirocin has been examined in a large multicentre trial which showed that the use of intra-nasal mupirocin in PD patients with confirmed nasal *S. aureus* carriage decreased exit-site infection but not peritonitis.[48] However, there is little data regarding the comparative efficacy between the intra-nasal *versus* exit-site application of mupirocin. While the use of mupirocin prophylaxis has resulted in reduced *S. aureus* infection in PD patients, *Pseudomonas aeruginosa* remains a significant issue for exit-site infections. A multicentre double-blind randomized trial compared the use of daily gentamicin ointment *versus* daily mupirocin ointment as exit-site prophylaxis. The results demonstrated that gentamicin ointment had similar efficacy for preventing *S. aureus* exit-site infection as mupirocin but with an added value of preventing *Pseudomonas* exit-site infections. Other emerging prophylactic therapies for PD exit site include the use of MediHoney and Polysporin triple (Bacitracin, gramicidin and polymixin B) ointment.[49–54]

Limitations

There is limited data regarding the comparative effectiveness between exit-site application *versus* intra-nasal application of mupirocin ointment.

Implementation issues

Adherence to proper hand hygiene during the care of PD catheter exit sites can be difficult, especially in elderly PD patients as well as health-care workers who work in PD centres with high patient load. The increasing prevalence of anti-microbial resistant organisms (especially methicillin-resistant *S. aureus*) also presents a significant problem in PD exit-site infections.

Audit items

The compliance to standard precautions and aseptic technique during the handling of PD catheter should be continuously audited. The rates and causative organisms (including antibiotics susceptibility) of PD catheter exit-site infections and peritonitis should also be regularly monitored. These data can help guide the change in exit-site prophylaxis policy in a PD unit.

D PREVENTION AND MANAGEMENT OF BLOOD BORNE VIRUS INFECTION

D1 General guideline statements

1. The renal unit should have in place a comprehensive blood borne virus (BBV) protocol to prevent the transmission, minimize the incidence, facilitate early detection and guide the management of BBV infections. [R]
2. Standard operating procedures with regular reinforcement should be in place to ensure strict compliance with infection control measures. [R]
3. A surveillance program should be in place to test for evidence of BBV infections in dialysis patients at regular intervals. [R]
4. Dialysis equipment should be designated and segregated according to HBV status, that is, labelled as 'HBV-positive' or 'HBV-negative'. Ideally, dialysis equipment should be designated and segregated according to hepatitis C virus (HCV) and human immunodeficiency virus (HIV) status especially in areas of high prevalence, but this may not be always feasible, and thorough disinfection and cleaning of equipment according to standard procedures, with strict adherence to standard precautions and infection control measures, is obligatory prior to their use on other patients. [R]

Comments

Major reasons for the transmission of BBV in dialysis units include breaches in standard precautions or infection control good practice, or failure to identify and isolate patients infected with BBV, especially the recently infected individuals.

D2 Serological screening for HBV, HCV and HIV

Guideline statements

1. hepatitis B s antigen (HBsAg), anti-HBs, anti-HBc (see Note below), anti-HCV, anti-HIV and alanine aminotransferase (ALT) level should be tested in dialysis

patients and in potential kidney transplant recipients at baseline, that is, prior to commencing dialysis, preferably at presentation. [R]
2. Testing for viral hepatitis markers (and other microbiological agents as clinically indicated) should be performed in susceptible individuals when there is clinical or biochemical evidence of hepatitis. [R]
3. In patients susceptible to HBV infection (i.e. who are negative for both HBsAg and anti-HBs), HBsAg is to be tested every 6 months in patients on HD [R], and annually in patients on PD [D]. In HD patients who are positive for anti-HBs antibody, testing for anti-HBs should be repeated annually and patients should be given a booster dose of HBV vaccine when anti-HBs level is below 10 IU/L. [R]
4. Patients with acute hepatitis B or C should have follow-up virological tests to determine whether they have developed immunity or have become long-term carriers. [R]
5. Testing for HCV RNA should be considered in anti-HCV negative dialysis or kidney transplant patients when HCV infection is strongly suspected [D], and is mandatory when the result informs treatment decisions. [R]
6. Since anti-HCV often remains persistently positive even after successful antiviral treatment, testing for HCV RNA in blood sample is required when it is necessary to determine the current HCV carrier status in such patients. [R]

Note

1. In patients who have tested negative for both HBsAg and anti-HBs but positive for anti-HBc, testing for HBV DNA should be performed. A patient who has tested negative for HBsAg and anti-HBs and HBV DNA, but positive for anti-HBc, should be dialyzed with an 'HBV-negative' HD machine, whereas a patient who has tested negative for HBsAg and anti-HBs, but positive for both anti-HBc and HBV DNA, should be dialyzed with an 'HBV-positive' HD machine, and segregated as such during HD.
2. When HD is urgently required in a patient who has tested negative for both HBsAg and anti-HBs –
   a. if the results of both anti-HBc and HBV DNA are not known, the patient should be dialyzed with an HD machine designated for patients with 'UNKNOWN HBV Status' when available. In units which only have 'HBV-positive' or 'HBV-negative' HD machines for the purpose of urgent HD, an 'HBV-negative' machine should be used; or
   b. if the patient is positive for anti-HBc but the result of HBV DNA is not known, the patient should be dialyzed with an HD machine designated for patients with 'UNKNOWN HBV Status' when available. In units which only have 'HBV-positive' or 'HBV-negative' HD machines for the purpose of urgent HD, an 'HBV-negative' machine should be used; and
   c. the 'HBV status' of the patient may need to be amended and updated when the results of both anti-HBc and HBV DNA are available.
3. HBV DNA may change from positive to negative as a result of treatment or spontaneously. A known chronic HBV carrier, based on serological profile or previous HBV

Summary of serological testing schedule for HBV, HCV and HIV in dialysis patients.

	Haemodialysis	Peritoneal dialysis	Comments
A. Prior to commencing dialysis			
All patients	HBsAg, anti-HBs, anti-HBc, anti-HCV, ALT, anti-HIV	HBsAg, anti-HBs, anti-HBc, anti-HCV, ALT, anti-HIV	a. HBV DNA test is indicated in HD patients who are HBsAg negative and anti-HBs negative but anti-HBc positive b. Testing for HBV DNA in subjects who are HBsAg negative, anti-HBs positive, and anti-HBc positive is done when clinically indicated, for example, when potent immunosuppressive treatment is being considered c. Irrespective of anti-HCV status, testing for HCV RNA is indicated to determine the current HCV carrier status in patients who have previously received anti-viral treatment
B. After commencing long-term dialysis			
Patients who are HBsAg negative and anti-HBs negative and anti-HBc positive or negative	HBsAg half-yearly	HBsAg annually	–
Patients who are HBsAg negative and with anti-HBs >10 IU/L	anti-HBs annually	anti-HBs annually	booster HBV vaccine advisable when anti-HBs ≤10 IU/L
Patients who are HBsAg positive	HBsAg annually	–	–
Patients who are anti-HCV negative	anti-HCV half-yearly	–	–
Patients who are anti-HCV positive	anti-HCV annually	anti-HCV annually	when HCV reactivation is suspected in known responders to prior HCV treatment, HCV RNA test is indicated irrespective of anti-HCV status
Patients either anti-HIV positive or negative	anti-HIV annually	–	–

DNA result tested outside the primary infection time-frame, should always remain in the category of 'HBV-positive', even when the latest HBV DNA status is negative (see summary table).

D3 Management of patients with HBV infection

Guideline statements

1. Regular monitoring of liver disease parameters and surveillance for HBV-associated complications are obligatory in patient management. [R]
2. HD patients who are chronic HBV carriers should be dialyzed with 'HBV-positive' machines and in segregated HBV-positive areas away from patients without HBV infection. [R]
3. Preventive antiviral treatment is necessary in patients with chronic HBV infection who are given potent immunosuppressive therapies, including immunosuppressive medications after kidney transplantation [R]. Currently, prophylactic treatment with entecavir is recommended. [R]

Comments

Patients with chronic HBV infection are at markedly increased risk of developing liver complications such as cirrhosis and hepatocellular carcinoma. It is therefore necessary to regularly monitor their liver status and to perform regular surveillance investigations for hepatocellular carcinoma including blood level of alpha-fetoprotein and liver imaging.

Both machine and spatial segregation are recommended for HD patients with chronic HBV infection since failure to do so has been associated with an increased incidence of HBV infection in the dialysis unit. HBV DNA may change from positive to negative as a result of treatment or spontaneously. A known chronic HBV carrier, based on serological profile or previous HBV DNA result tested outside the primary infection time-frame, should always be regarded as 'HBV-positive', even when the latest HBV DNA status is negative.

HBV-associated liver disease is often relatively stable in patients on long-term dialysis, but immunosuppression can precipitate HBV reactivation and accelerate liver disease progression. Preventive antiviral therapy for patients infected with HBV who are given immunosuppressive medications can be administered as prophylactic treatment commencing at the time of immunosuppression or as preemptive treatment upon detection of increased viral replication as evidenced by increasing HBV DNA levels in serial blood samples. However, the latter approach should only be adopted when there is access to frequent HBV DNA assays with a rapid turn-around time. Under the setting of a busy clinical service, the prophylactic approach is preferred. Presently entecavir is the preferred antiviral treatment for HBV in patients with renal diseases because of its high efficacy and high barrier to the development of drug resistance and also renal safety.

D4 Management of patients with HCV infection

Guideline statements

1. Sero-positivity for HCV RNA by polymerase chain reaction (PCR) assay is required for the diagnosis of current (active) HCV infection. Testing for HCV RNA is advisable in patients in whom HCV infection is strongly suspected based on clinical grounds but who are sero-negative for anti-HCV, since a low percentage (<5%) of patients with impaired immunity may be anti-HCV negative but HCV RNA positive. [D]
2. Patients with a history of viral clearance after prior HCV infection, either spontaneous or consequent to therapy, can remain sero-positive for anti-HCV for many years, and testing for HCV RNA is required to diagnose HCV recurrence or reinfection. [R]
3. Though not obligatory, machine and spatial segregation is preferred for HCV-infected HD patients in a dialysis unit, especially in units with a relatively high prevalence of HCV sero-positivity. [D]
4. Quantitation of circulating HCV RNA level is necessary before starting antiviral treatment. [R]
5. In patients with active HCV infection, testing for HCV genotype(s) is recommended to guide the selection of antiviral treatment [R]. It is also desirable to assess liver fibrosis by non-invasive means before treatment. [D]
6. The field of direct-acting antiviral (DAA) regimens for the treatment of HCV infection is evolving rapidly. Treatment decisions take into account HCV genotype, efficacy and tolerability, affordability and confounding patient characteristics, and require input from hepatologists and patient counselling. [R]
7. Patients with severe manifestations of HCV-associated liver disease, including fibrosing cholestatic hepatitis, or extra-renal manifestations, such as cryoglobulinemic syndromes or renal manifestations, are ascribed higher priority when considering antiviral treatment. [D]
8. Regular monitoring of liver disease status and surveillance for HCV-associated complications are obligatory in patient management. [R]

Comments

In HD units, both horizontal transmission (between patients in the same unit not sharing HD machines) and vertical transmission (between patients sharing HD machines) of HCV infection have been reported. However, inadequate infection control practices rather than machine or space segregation were often the main reasons for these outbreaks.

Machine and/or spatial segregation are encouraged, if deemed feasible, for HCV-infected HD patients.

In Hong Kong, the HCV carrier rate in the general population is below 0.5%. There is marked geographical variation in the distribution of HCV genotypes globally, and 1b is the predominant genotype in patients on renal replacement therapies in Hong Kong, although other genotypes have also been detected and mixed infection by different genotypes can occur.

Previous standard treatment for HCV comprising pegylated interferon and ribavirin, which was associated with suboptimal efficacy and considerable adverse effects especially in patients with kidney diseases, are being replaced with oral DAA, which demonstrate much improved efficacy in achieving viral eradication. DAA drugs for the treatment of HCV infection are protease inhibitors or polymerase inhibitors that target different steps in the viral life-cycle, such as post-translation processing of polyproteins and RNA replication, respectively. There are ongoing studies on different DAA treatment regimens and the field is evolving rapidly with the availability of new data. Treatment efficacy and the optimal combination regimen and/or duration vary according to HCV genotypes.

Similar to HBV, immunosuppressive treatment can precipitate HCV reactivation and disease flare. However, there is relatively little data on preventive antiviral therapy for patients with kidney diseases who are infected with HCV. The timing and choice of treatment under such circumstances are to be individualized and require input from hepatologists.

D5 Management of patients with HIV infection

Guideline statements

1. Machine and spatial segregation is preferred, but not obligatory, for HIV-infected HD patients. [D]
2. Irrespective of machine designation, it is advisable to separate HIV-infected subjects from susceptible patients during HD. [D]
3. HIV-infected patients should be under the care of a relevant infection specialist team and managed according to prevailing standards. [R]

D6 Management of newly diagnosed BBV infection

Guideline statements

1. Subjects with confirmed acute BBV infection should be treated according to current standard-of-care regimens, such as entecavir for HBV and DAA for HCV. [R]
2. Patients with newly diagnosed BBV infection should be counselled with regard to the disease course and its complications and infection control measures, and the source of infection investigated. [R]
3. When there is a newly diagnosed BBV infection in a dialysis unit, testing for the respective BBV infection should be conducted in other patients who have a risk of BBV exposure, such as those who have shared dialysis session or machine with the newly infected index case. [R]

D7 Management of patients or staff with BBV exposure

Guideline statements

1. Reporting of incident(s) of BBV exposure should follow prevailing institutional guidelines. [R]
2. In cases of inadvertent exposure to potentially infectious material, the source and the exposed person (patient or staff) should be tested for the status of BBVs. [R]
3. Susceptible persons exposed to the risk of BBV infection should be counselled to adopt precautionary measures to prevent secondary transmission until investigations confirmed no transmission of infection due to the exposure. [R]
4. Susceptible patients or staff, and subjects with unknown HBV status, who have exposure to HBV should be tested for HBsAg, anti-HBs, anti-HBc and ALT levels immediately after exposure. HBsAg status should be tested again at 4, 8 and 12 weeks after exposure to ascertain whether infection has occurred. [R]
5. Susceptible patients or staff members who have inadvertent exposure to potential HBV infection should receive timely hepatitis B immune globulin and vaccination [R]. In subjects given both HBV vaccine and hepatitis B immune globulin the anti-HBs response can only be reliably ascertained after at least 4 months. [R]
6. Anti-HBs status should be tested when a subject exposed to potential HBV infection has prior HBV vaccination but unknown anti-HBs response. No treatment is necessary if anti-HBs level is adequate (i.e. above 10 IU/L), while hepatitis B immune globulin and vaccine booster should be given when the anti-HBs level is inadequate. [R]
7. Interferon with or without ribavirin are not recommended as post-exposure prophylaxis for HCV. [R]
8. Susceptible patients or staff who have inadvertent exposure to HCV should be tested for anti-HCV, HCV RNA and ALT levels immediately after exposure, with repeat testing for HCV RNA after 4 weeks and repeat testing for anti-HCV after 16 and 24 weeks to ascertain whether infection has occurred [R]. Hepatologists should be consulted for further management.
9. Patients or staff who have inadvertent exposure to HIV should be given prophylactic antiretroviral treatment, the current recommendation for which is a three-drug regimen for 4 weeks, and the choice of medications

should take into consideration the drug susceptibility/resistance status of the virus in the source person. [R]
10. Susceptible patients or staff who have inadvertent exposure to HIV should be tested for anti-HIV status immediately after exposure, with repeat testing after 6 weeks, 12 weeks and 6 months [R]. When the source is coinfected with both HIV and HCV and the exposed person has acquired HCV after the exposure incident, extended follow-up testing for anti-HIV up to 12 months is recommended. [R]
11. Patients who have received dialysis, blood products, or kidney allograft with uncertain BBV status, including having such procedures outside Hong Kong, should be regarded as exposed to potential BBV infection and managed accordingly. [R]

Comments

It is desirable that staff members be tested for HBsAg and anti-HBs before joining the renal unit, and HBV vaccination is recommended for individuals who are susceptible to HBV infection (HBsAg and anti-HBs both negative). It is advisable that staff members who are sero-negative for anti-HBs be tested for HBsAg status at least annually. It is advisable that HBV-infected staff members refrain from carrying out invasive procedures in patients who are susceptible to HBV infection.

Testing for anti-HCV in staff need not be routine in our locality in view of the low HCV carrier rate in the general population, but is recommended in individuals with identifiable risk factors for HCV infection or a history of non-A non-B hepatitis. Similar to the case for HBV, it is advisable that HCV-infected staff members refrain from carrying out invasive procedures in patients who are susceptible to HCV infection.

When HBV infection occurs after exposure to HBV, seroconversion to become HBsAg-positive occurs anytime between 1 and 9 weeks after exposure. Subjects may recover from the acute infection with clearance of HBsAg from blood and production of anti-HBs, the latter being detectable months after the onset of infection, or may become long-term HBV carriers.

In acute HCV infection, there is an initial 'eclipse phase' lasting 1–2 weeks during which HCV RNA is not yet detectable in blood. Also, HCV RNA level may fluctuate during the early course of infection. Anti-HCV is usually detectable anytime between 8 and 12 weeks after infection, often after the onset of symptoms or abnormal liver enzyme levels. The time interval from infection to sero-positivity for anti-HCV is termed the 'window period'. Sero-positivity for anti-HCV does not distinguish between acute infection and chronic infection.

While interferon, with or without ribavirin, is not recommended as post-exposure prophylaxis for HCV, and there is little data on DAAs in this regard, it is reasonable to consider DAA therapy in the exposed person. Hepatologists should be consulted with regard to further management.

It is recommended that post-exposure prophylactic treatment for HIV includes a minimum of three antiretroviral drugs for 4 weeks. However, some subjects may not be able to complete the full treatment duration due to poor drug tolerability. Opinion on the treatment of patients should be sought from an infectious disease specialist.

D8 Immunization

Guideline statements

1. Immunization programs should be in place to ensure that patients with kidney diseases are vaccinated early in the course of progressive renal impairment to maximize the chance of achieving protective immunity. [R]
2. Live or live-attenuated vaccines must not be administered to immunosuppressed patients including kidney transplant recipients [R], and are not preferred in patients with moderate to severe renal impairment. [D]
3. HBV vaccination is indicated in patients with chronic kidney diseases who are sero-negative for both HBsAg and anti-HBs [R]. Testing for anti-HBs antibody response should be performed 2–3 months after completion of the vaccination schedule. [R]
4. In dialysis patients who have a history of sero-positivity for anti-HBs, reassessment of anti-HBs status annually is indicated for patients on HD [R], and is advisable for patients on PD or after kidney transplantation [D]. It is desirable that booster HBV vaccine be administered when anti-HBs level is less than 10 IU/L. [D]
5. The dose of HBV vaccine should be doubled in patients with moderate to severe renal impairment and in immunosuppressed kidney transplant recipients. [R]
6. Influenza vaccination is recommended in patients with moderate to severe renal impairment, patients on dialysis, and kidney transplant recipients. [R]
7. Pneumococcal vaccination reduces the incidence of invasive pneumococcal disease and is recommended for patients with chronic kidney disease or nephrotic syndrome and for kidney transplant recipients. [R]

Comments

HBV – Compared with immunocompetent adults, in whom adequate anti-HBs response occurs in over 95% after HBV vaccination, the immunization efficacy is reduced (median 60–70%) in dialysis patients and immunosuppressed kidney transplant recipients. Patients should be vaccinated according to the standard intramuscular schedule over 6 months, and the dose should be doubled in patients with moderate to severe renal impairment, patients receiving immunosuppressive medications, and kidney transplant recipients. In patients who are scheduled to undergo kidney transplantation within 6 months, an accelerated vaccination schedule with three to

four doses of vaccine given monthly can be considered. In non-immune kidney transplant recipients, delaying HBV vaccination for 6–12 months after the transplant operation may increase the immunization efficacy. HBV infection has been observed in dialysis patients with prior anti-HBs response after vaccination but whose prevailing anti-HBs level was below 10 IU/L. Therefore, booster dose of HBV vaccine is recommended for patients with prior anti-HBs but whose anti-HBs level has fallen to 10 IU/L or below. Subjects who have not responded to one course of HBV vaccination should be given another course of vaccine, and if it still fails to induce anti-HBs additional dose of vaccine is not warranted.[55–62]

Influenza – Patients with moderate to severe renal impairment and immunosuppressed subjects including kidney transplant recipients should receive annual influenza vaccination with inactivated vaccine, not live-attenuated vaccine, prior to commencement of influenza activity in the local community.

Pneumococcal – Pneumococcal vaccination reduces the incidence of invasive pneumococcal disease such as bacteremia, meningitis and empyema, and it reduces the severity of virus-associated pneumonia with pneumococcal co-infection. Pneumococcal vaccination is recommended for all adults at or above the age of 65 years and for subjects of age 19–64 years at increased risk of pneumococcal disease or its complications, including patients with anatomic or functional asplenia, chronic kidney disease, nephrotic syndrome or after kidney transplantation. Patients who have not previously received 23-valent pneumococcal polysaccharide vaccine (PPSV23) or 13-valent pneumococcal conjugate vaccine (PCV13) should receive one dose of PCV13 first, followed by one dose of PPSV23 8 weeks later, and one more dose of PPSV23 5 years later. Patients who have previously received PCV13 only should be given PPSV23 as described above. Patients who have previously received one or more doses of PPSV23 only should be given one dose of PCV13 at 1 year or more after the last dose of PPSV23.

E INFECTION PROPHYLAXIS IN THE KIDNEY TRANSPLANT RECIPIENTS

E1 Pre-transplant evaluation and immunization

Introduction

Infection is a common and important complication in kidney transplantation recipients (KTR), and is associated with appreciable patient morbidity and mortality.[63,64] Infection in KTR can be donor-derived or reactivations of previous infections. Hence, infection screening of both the donors (live and deceased) as well as the recipients constitutes a key role in the prevention of post-transplant infections. The difference between infection screening for live donor and deceased donor transplantation is related to time constraints. For live donor kidney transplantation, clinicians have ample time to screen and treat infections, to decline unsuitable donors, and find other potential donors if necessary. In deceased donor kidney transplantation, in the interest of time, testing is often limited to serological methods which are readily available and with fast turn-around time. While proper screening can minimize post-transplant infective risks, immunization can also serve as an effective means to prevent post-transplant infectious disease.

Guideline statements

E1.1. HBsAg, anti-HBs, anti-HBc, anti-HCV, anti-HIV, serology for cytomegalovirus (CMV), Epstein Barr Virus (EBV) and Varicella Zoster Virus (VZV) and syphilis venereal disease research laboratory (VDRL) should be checked in both the donor and recipient before kidney transplantation. (R)

E1.2. hepatitis B e antigen (HBeAg) and HBV DNA should be checked in HBsAg-positive patients before kidney transplant. (R)

E1.3.Chest radiography should be performed in all recipients for kidney transplantation to look for latent tuberculosis (TB) infection. (R)

E1.4. Patients who are HBsAg and anti-HBs negative should receive HBV vaccination before kidney transplantation. (R)

Rationale

The HBV and HCV should be ascertained in the donor and recipient before renal transplantation. HBV infection confers adverse outcomes in KTR due to acute hepatic complications such as fulminant hepatitis/fibrosing cholestatic hepatitis or chronic complications such as cirrhosis and hepatocellular carcinoma.[65,66] Careful matching of the donor/recipient HBV status is an important step to prevent HBV transmission during renal transplantation. Chronic HBV infection in the recipient is not a contraindication of kidney transplantation. In HBsAg-positive transplant candidates, the HBeAg and HBV DNA levels should also be evaluated as HBeAg positivity and high HBV DNA levels are associated with increased risk of HBV reactivation after renal transplantation.[67] Renal transplantation when both donor and recipient are both HBsAg-positive is also possible, especially in localities with high prevalence of HBV carrier and organ shortage. The use of the HBsAg negative but anti-HBc positive donor is slightly more complex. The risk of transmission to kidney recipients appears to be low though has been reported.[68,69] Such risk can be further reduced by pre-transplant HBV vaccination, use of HBV immunoglobulin (HBIG) and/or in combination of oral nucleostide/tide analogues.[70–72] HBV vaccination is an effective means to prevent HBV transmission and hence should be administered to dialysis patients who are HBsAg-negative and anti-HBs negative. The efficacy of HBV vaccine might be reduced in renal failure and higher dose of vaccine is advocated.[73] Intradermal HBV vaccine can be considered in patients who fail to mount protective antibodies (i.e. anti-HBs) after standard HBV immunization.[74]

The risk of transmission of HCV infection associated with organ transplantation from an HCV-positive donor is high, and HCV-negative recipients who received an HCV-positive kidney had significantly adverse outcomes.[75,76] These data suggested a HCV-positive kidney should not be transplanted to a HCV-negative recipient. It remains optimistic that advances in donor/recipient matching with respective to genotypes and the use of novel anti-HCV treatments may further improve the safety of these HCV-positive renal transplants in the future.

Human immunodeficiency virus infection in the recipient is previously considered a contraindication for renal transplantation. Mounting evidence has suggested that such renal transplantation in carefully selected patients can be associated with acceptable clinical outcomes. A prospective study have examined the outcomes of renal transplantation in 150 HIV-positive recipients who had CD4+ T-cell counts greater than 200/cm^3 and undetectable HIV RNA.[77]

The CMV and VZV serological status of donor and recipient will help determine the risk of post-transplant infection and hence guide clinician decisions for prophylaxis. The prophylactic strategies for CMV and VZV will be discussed in subsequent sections. EBV is highly associated with post-transplant lymphoproliferative disease (PTLD).[78] Transmission of syphilis by renal transplantation and has been reported and syphilis infection can have severe clinical manifestation in renal transplant recipients.[79] Nevertheless, syphilis is not a contraindication of renal transplantation if each recipient receives an appropriate course of post-transplant penicillin.[79]

Tuberculosis is endemic infection in the Asia-Pacific region. TB infection in KTR is associated with substantial mortality (~20–30%) and the majority of cases are due to reactivation of old infective foci.[80,81] Chest radiography should be performed in all recipients to exclude latent or old TB, especially in localities where TB is endemic.[82] The detection of these radiological abnormalities will prompt clinicians to use isoniazid prophylaxis.[83]

Limitations

Donors with high risk of HIV or HCV might have false-negative results during the window period and more sensitive tests such nucleic acid-based assays might be warranted. These sensitive tests, however, might give rise to false positive results and hence limit organ availability. VDRL can also give rise to false-negative and false-negative results, and more accurate tests might lead to resource implications and slower turn-around time. Limitation of using skin tuberculin tests to screen latent TB include: (i) most Hong Kong people have previous bacillus calmette–guérin (BCG) vaccination and hence skin tuberculin tests are often false-positive; (ii) impaired immunological response dialysis patients can give rise to false-negative skin tuberculin test results. There is also limited local experience regarding renal transplantation in HIV-positive recipients.

Implementation issues

Nucleic acid based tests for viral infections and interferon-gamma release assays for latent TB might be an alternative but the costs remain significant hindrance to its widespread application in different centres in Hong Kong.

Audit measures

The rate of donor-derived infection and reactivation of previous infections should be regularly monitored and audited. A changing pattern of disease might warrant modifications in strategy for donor/recipient screening and prophylaxis.

E2 Peri-transplant antimicrobial prophylaxis

Introduction

Peri-operative antibiotics prophylaxis remains a cornerstone for the prevention of early post-transplant infections. While conventional perioperative antibiotics prophylaxis protocol had been adopted widely in various centres, novel antibiotics have been introduced to provide enhanced efficacy and spectrum of coverage to prevent early post-transplant infections.[84–86]

Guideline statements

E2.1. A second or third generation cephalosporin should be used as peri-transplant antibiotics prophylaxis and discontinued within 24 h. (R)

Background

There is a paucity of randomized studies to address the need for peri-transplant antibiotics prophylaxis. While Cohen *et al*. reported a reduction in post-transplant infections during the first 5 days among patients who received peri-transplant antibiotics prophylaxis when compared with those who did not receive antibiotics prophylaxis (11 *vs* 42%),[85] others had shown a similar rate of urinary tract infection (UTI) in KTR with or without peri-transplant antibiotics prophylaxis.[87] In this regard, one large study had observed high rates of UTI (73.7%) in KTR who did not receive peri-transplant antibiotics prophylaxis.[88] In a Europe-wide survey, 83% of the transplant centres had adopted a peri-transplant antibiotics protocol with second or third generation cephalosporins being the most commonly used antibiotics.[89]

Limitations

There is lack of prospective randomized trial data to suggest the clinical benefit of peri-operative antibiotics prophylaxis. The variable length of observation for post-transplant infections among different studies had made comparison of results difficult and inconclusive. Furthermore, the use of second or third generation cephalosporins is associated with selection of multidrug-resistant organisms (MDRO).

Implementation issues

Dialysis patients on transplant-waiting list are of escalated risk of MDRO. The use of second or third generation cephalosporins may be ineffective in centres with high rates of extended spectrum beta-lactamase (ESBL)-producing organisms or multidrug-resistant pathogens.

Audit measures

The rates and types of early post-transplant infections should be periodically reviewed. These data will help evaluate the efficacy of the current peri-transplant antibiotics regimen.

E3 Post-transplant antimicrobial prophylaxis

E3.1 Cytomegalovirus

Cytomegalovirus is one of the most common and important viral infections among KTR. Important risk factors for CMV reactivation after solid organ transplantation include recent intensification of immunosuppressive regimen and the use of lymphocyte-depleting agents.[90,91] The approach to CMV prevention varies between patients and is dependent on individual's risk profile.

Guideline statements

E3.1.1. CMV pp65 antigen or PCR should be used for the rapid diagnosis of CMV disease. (R)

E3.1.2. CMV pp65 antigen should be monitored at least weekly for 12 weeks after renal transplantation when a pre-emptive approach is adopted. (D)

E3.1.2. Prophylactic oral valganciclovir should be used in D+/R− cases or those who receive anti-thymocyte therapy (either as induction or anti-rejection treatment) for at least 6 months. Oral or IV ganciclovir can be considered as alternatives for oral valganciclovir. Close surveillance for CMV disease is mandatory after stopping prophylactic treatment. (R)

E3.1.3. Both pre-emptive and prophylactic approach can be considered in renal transplant recipients who are CMV seropositive. (D)

E3.1.4. For the pre-emptive approach, valganciclovir (900 mg bd PO) or IV ganciclovir (5 mg/kg, q12h) should be initiated when CMV pp65 > 40 positive cells/2×10^5 cells and be discontinued when two consecutive weekly CMV pp65 antigen sample has become negative. (R)

Rationale

The CMV pp65 antigen served as good assay for the diagnosis of CMV disease and also for the monitoring of therapeutic response.[92] It has the advantage of rapid turn-around time and high sensitivity.[92] One disadvantage of CMV pp65 assay is the false-negative results when patients suffered from leucopenia.[92] In this context, nucleic acid tests such as CMV PCR might better reflect CMV replication.[92,93] In fact, quantitative nucleic acid tests are growing in popularity as methods for the diagnosis of CMV infection after solid organ transplantation. Viral culture show high specificity for diagnosis of CMV infection. However, its application is limited by its modest sensitivity and slow turn-around time which rendered this test unfavourable for guiding treatment decisions.[92]

The prophylactic approach refers to the prescription of anti-viral agent to all 'at-risk' patients for a defined period after solid organ transplantation, and regardless of the CMVpp65 antigen or CMV PCR results. Oral valganciclovir, oral or IV ganciclovir and oral valacyclovir are all effective prophylaxis for CMV infection.[94–97] While all three agents have shown efficacy in randomized clinical trials, valganciclovir is the preferred prophylaxis for CMV infection. In one randomized controlled trial which compared valganciclovir and ganciclovir, both drugs have demonstrated similar efficacy in preventing CMV disease (17.2 *vs* 18.4%).[94] In this context, valganciclovir has the advantage of good bioavailability and lower pill burden. The clinical benefit of valganciclovir was further supported by another prospective randomized trial which included 318 CMV D+R− kidney transplant recipients. This study compared the different treatment duration of valganciclovir (100 *vs* 200 days), and concluded that the latter was associated with significantly lower incidence of CMV disease (36.8 *vs* 16.1%).[98] Based on these results, the prophylactic approach is preferred in KTR who are D+R− and a 200-day course of valganciclovir appeared to be the optimal prophylaxis. Compared with the pre-emptive approach, the efficacy of the prophylactic approach was supported by more large randomized trials and was associated with clinical benefits on graft outcomes, mortality and other opportunistic infections.[99] However, the prophylactic approach was also associated with higher treatment costs and increased risk of myelosuppression and late-onset CMV disease. The pre-emptive approach refers to regular monitoring of viral replication and initiation of anti-viral treatment when a certain virological threshold is reached. The prerequisite of pre-emptive include good coordination of patients for regular monitoring and fast turn-around time of laboratory tests. Oral valganciclovir and IV ganciclovir are both effective agents for pre-emptive treatment in asymptomatic CMV reactivation.[100,101] Other merits of the pre-emptive approach include lower drug costs and potentially less treatment toxicity with shorter duration of anti-viral therapy.

Limitations

There is a paucity of data to compare the impact of prophylactic and pre-emptive approaches on long-term clinical outcomes such graft and patient survival. The optimal threshold for initiation of anti-viral therapy for the pre-emptive approach remained to be determined.

Implementation issues

Adoption of the pre-emptive approach requires fast turn-around time of CMV pp65 assays. The coordination of regular blood monitoring schedules also imposes substantial resource implications to a renal transplant unit. The use of prophylactic approach will incur increased drug budget in a nephrology unit, especially when oral valganciclovir is used as the prophylactic anti-viral agent. The high drug cost of valganciclovir also remains a hindrance to its widespread use in local renal centres.

Audit measures

Each renal unit should develop its own protocol for CMV disease monitoring and treatment. The rate of CMV disease in the renal transplant unit should be regularly audited and the preventive strategy for CMV be modified accordingly.

E3.2 Pneumocystis jiroveci

Introduction

Pneumocystis jiroveci pneumonia (PCP) classically presents with fever and dyspnoea in immunocompromised hosts and is associated with high mortality in KTR.[102] The incidence of PCP has decreased over years due to the judicious use of corticosteroids and effective prophylactic measures in KTR, but the overall incidence still ranged between 3 and 5%.[103]

Guideline statements

E3.2.1. All KTR should receive PCP prophylaxis for at least 6 months after transplantation. (R)

E3.2.2. Patients who has received anti-thymocyte therapy or has recent intensification of immunosuppression for allograft rejection should receive PCP prophylaxis. (R)

E3.3.3. Cotrimoxazole is the drug of choice for PCP prophylaxis in patients with normal glucose-6-phosphate dehydrogenase (G6PD) status.

E3.3.4. Aerosolized pentamidine (300 mg per month) can be used in patients with G6PD deficiency or allergy to co-trimoxazole. (D)

E3.3.5. When aerosolized pentamidine is not available, Tripmethoprim can be considered as second line prophylaxis for PCP infection in patients with G6PD deficiency or allergy to co-trimoxazole.

Rationale

PCP prophylaxis should be initiated in all KTR for at least 6 months after transplantation.[102–104] PCP prophylaxis should also be used in patients who had received anti-thymocyte therapy or had recent intensification of immunosuppression for allograft rejection.[102–104] In this context, cotrimoxazole is the drug of choice for PCP prophylaxis in patients with normal G6PD status.[102,105] Other potential benefits of cotrimoxazole include its efficacy for the prevention of toxoplasmosis and UTI. Inhalational pentamidine should be considered in patients with G6PD deficiency.[106] Pentamidine is generally well tolerated but is associated with higher incidence of breakthrough infections when compared with cotrimoxazole.[102,107] Other options of PCP prophylaxis include dapsone, atovaquone, as well as clindamycin and pyrimethamine.[102]

Limitations

Recent studies have suggested that late-onset PCP can occur several years after transplant recipients who have discontinued prophylaxis.[108] Whether the duration of PCP prophylaxis in KTR should be extended remains unclear, and the decision to prolong the duration of PCP prophylaxis should be individualized.

Implementation issues

There is limited choice for PCP prophylaxis when a KTR is G6PD-deficient. In this context, aerosolized pentamidine can be used as an alternative but is limited by the increased risk of breakthrough infections.

Audit measures

The incidence and timing of PCP infection should be regularly reviewed. Extending the duration of PCP prophylaxis might be considered if rising incidence of late-onset PCP infection is observed.

E3.3 Herpes zoster

Introduction

The majority of VZV infections in KTR is due to reactivation of VZV and presents as herpes zoster (shingles) which is usually confined to a single dermatome.[109–111] Occasionally, KTR who receive intensive immunosuppression (e.g. recent anti-rejection therapy) can also develop disseminated zoster infections with visceral involvement.

Guideline statements

E3.3.1. Oral acyclovir or its prodrugs (e.g. valacyclovir) are effective prophylaxis for VZV infection and can be considered in herpes simplex virus (HSV)-positive patients who are not receiving CMV prophylaxis. (D)

E3.3.2. Routine long-term prophylaxis for VZV reactivation after renal transplantation is not recommended. (R)

E3.3.3. VZV vaccine can be safely administered in dialysis patients but should not be used in KTR. (R)

E3.3.4. Post-exposure prophylaxis with intravenous immunoglobulin (IVIG) or acyclovir can be considered in seronegative KTR. (D)

Rationale

The evidence regarding the use of acyclovir prophylaxis is primarily derived from data in other immunocompromised populations.[112] Data which focuses on the efficacy of

acyclovir in KTR is lacking. In some renal units, acyclovir is already used for CMV prophylaxis after kidney transplantation and this also offer some protective effects against VZV and other herpes viruses. Short-term prophylaxis with acyclovir can be given to HSV-positive KTR who are not receiving CMV prophylaxis during the early post-transplant period.[113] There is inadequate data to suggest routine long-term administration of VZV prophylaxis in KTR.[113] There is also no guidelines regarding VZV prophylaxis after recent intensification of immunosuppressive treatments (e.g. for allograft rejection).

VZV vaccine, being a live vaccine, poses a risk of disseminated infection in KTR and thus is contraindicated in KTR.[113] Seronegative KTR are vulnerable to severe primary infection and hence should receive post-exposure prophylaxis after significant exposure to VZV. Options for post-exposure prophylaxis include passive immunization and/or anti-viral agents. While varicella zoster immunoglobulin (VZIG) is not available in many centres, IVIG appear to be a reasonable alternative as post-exposure prophylaxis.[113,114] The efficacy of anti-viral agents, when used as adjunct to VZIG, has been demonstrated in immunocompetent children and in a small study of high-risk children (five being KTR).[115–117] However, the use of acyclovir as post-exposure prophylaxis in immunocompromised hosts has not been investigated in randomized controlled trials.

Limitation

VZV immunization has limited impact on the prevention of post-transplant VZV infection as most cases are related to reactivation. There is inadequate data to suggest routine long-term oral anti-viral agents for VZV prophylaxis.

Implementation issues

The use of IVIG as post-exposure prophylaxis is associated with increased drug budget in a renal unit.

Audit measures

The incidence of VZV primary infection or reactivation should be regularly monitored. Such data will help evaluate the current strategy for VZV prophylaxis in KTRs in a renal unit.

E3.4 Tuberculosis

Introduction

TB infection in post-transplant recipients is associated with mortality as high as 20–30% and most cases are related to reactivation of old infective foci.[81,118] The diagnosis and treatment of TB reactivation are often difficult. These diagnostic challenges stem from the atypical clinical manifestations as well as inconclusive or negative test results despite active disease. Therapeutic difficulties often arise from treatment toxicities, drug resistance and potential interactions with immunosuppressive agents. Against these backgrounds, prevention of post-transplant TB reactivation is therefore worthwhile and can potentially improve patient outcomes.

Guideline statements

F3.4.1. Prophylactic isoniazid (300 mg daily) should be administered for 1 year in KTR with known previous history of TB infection. (D)

F3.4.2. Renal transplant candidates awaiting deceased donor kidney and with recent exposure or tuberculin skin test conversion should be evaluated and treated before transplantation. (D)

Rationale

One retrospective study in Hong Kong had demonstrated that isoniazid (300 mg daily) given for 12 months can effectively prevent TB reactivation in Chinese patients with previous history of TB, and such regimen is safe and well tolerated.[83] Oral pyridoxine should be prescribed with prolonged administration of isoniazid to prevent peripheral neuropathy.[82,83] Rifampicin given as prophylaxis for 4 months is not preferred due to limited data on its efficacy and it can significantly reduce the drug level of calcineurin inhibitors.[119] Dialysis patients on transplant waiting list have long waiting time in this locality and renal failure itself is an important risk factor for TB.[82] Thus, dialysis with recent exposure or tuberculin skin test conversion (i.e. from negative to positive) should be thoroughly evaluated and treated before transplantation.[82] Patients who receive prolonged isoniazid treatment should have their liver function regularly monitored although the reported risk of isoniazid-induced hepatoxicity in KTR is not higher than that in the general population.[83,120]

Limitations

While tuberculin skin test is associated with increased false-positive rates in endemic areas, it is not uncommon to have false-negative results due to anergy in renal failure patients. Therefore, it remains difficult to detect latent TB and high index of suspicion might be required. Furthermore, there is also growing concern of drug-resistant TB which limits the efficacy of isoniazid prophylaxis.

Implementation issues

The prolonged administration of isoniazid is often associated with tolerability issues such as poor appetite, nausea, vomiting and hepatotoxicity.

Audit measures

The incidence, prevalence, site and susceptibility pattern of TB infection in KTR should be periodically audited. The data will help evaluate and modify current strategy of TB prophylaxis and monitoring in a nephrology unit.

E3.5 Others (invasive fungal infections)

Introduction

Invasive fungal infection is associated with adverse graft and patient survival, as well as high treatment costs in KTRs.[121,122]

Guideline statements

E3.5.1. Routine long-term anti-fungal prophylaxis is not recommended in KTRs. (R)

E3.5.2. Oral nystatin or clotrimazole lozenges for 1–3 months can be considered in KTRs to prevent oropharyngeal candidiasis. (D)

Rationale

The risk of invasive candidiasis or aspergillosis is low after isolated kidney transplantation and there is insufficient data to recommend routine anti-fungal prophylaxis in KTRs.[121–123] The kidney disease: improving global outcomes (KDIGO), guidelines have suggested the use of oral nystatin or clotrimazole lozenges for prevention of oropharyngeal candidiasis in KTRs.[124] However, the use of azoles as anti-fungal prophylaxis in KTRs is also hindered by potential drug–drug interactions and high treatment costs.

Limitations

Although oral nystatin might be a relative cheap and safe prophylaxis for oropharyngeal candidiasis, its efficacy for other invasive fungal infections remains relatively limited. The overall risk of invasive fungal infection in KTRs is low and hence the need for anti-fungal prophylaxis remains debatable.

Implementation issues

Nystatin is only effective for the prevention for *candida* infections but has no activity against *Aspergillosis* and other fungal species. The use of azoles in KTRs should be dealt with caution due to its interaction with post-transplant immunosuppressive treatments. The novel azoles such as voriconazole and posaconazole are very effective agents with broad anti-fungal spectrum, but their high costs and potential drug–drug interaction remain important hindrance for their use as prophylaxis in most nephrology units.

Audit measures

The incidence of invasive fungal infection in a renal transplant unit should be regularly monitored. A rising incidence of invasive fungal infection should prompt the review of immunosuppressive protocols, infection control measures and the need for anti-fungal prophylaxis in a nephrology unit.

F PREVENTION AND MANAGEMENT OF MULTIDRUG-RESISTANT ORGANISM

F1 Screening

Introduction

Resistance to multiple antibiotics occurs in different pathogens and is a growing concern for patient management in Renal Units. Examples of these MDRO include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant gram-negative bacilli (MDR-GNB), carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), multidrug-resistant tuberculosis (MDR-TB) and *Clostridium difficile*.[125] The prevention of MDRO infections can help improve patient outcomes and reduce overall health-care costs. In this context, the identification of patients colonized with MDRO constitutes the first step to prevent MDRO transmission within a dialysis unit.

Guideline statements

F.1.1. Screening for MDRO is recommended for dialysis patients for the following situation:

1) During an outbreak (defined as ≥2 new isolates of a MDRO identified from clinical specimen and related in time and place);
2) Dialysis patients who have been admitted or received dialysis services within the previous 6 months in an overseas hospital;
3) Dialysis patients who have recently been admitted to a ward/unit where recent MDRO outbreak was suspected or confirmed.

Rationale

Screening should be considered in situations deemed high risk of MDRO transmission.[126,127] These situations include: (i) during an outbreak (defined as ≥2 new isolates of a MDRO identified from clinical specimen and related in time and place); (ii) dialysis patients who have been admitted or received dialysis services within the previous 6 months in an overseas hospital; (iii) dialysis patients who have recently been admitted to a ward/unit where recent MDRO outbreak was suspected or confirmed. Appropriate clinical samples (e.g. wound or nasal swab for MRSA, rectal swabs for VRE and CRE, and urine for MDR-GNR) should be sent for the identification of MDRO. The institution of a screening program should be balanced against effectiveness and the resource implications.

Limitations

There is limited data regarding the optimal and cost-effective strategy for screening MDRO in dialysis patients.

Implementation issues

MDRO surveillance poses significant resource implications on dialysis units. Adherence to screening protocols can be difficult in dialysis units with high patient load and turnover.

Audit measures

Cases of MDRO infection should be properly documented and reviewed periodically. Clustering of MDRO cases should prompt investigation for outbreaks and breach of infection-

control measures. The need for surveillance cultures of MDRO in a dialysis unit should be based on these audit results and changes in local bacteriology.

F2 Management of patients infected or colonized with a MDRO

F2.1 Methicillin resistant *Staphylococcus aureus*

Introduction

In a national survey of dialysis centres in United States, MRSA strains accounts for more than 40% of isolates of *S. aureus.*[128] Risk factors for MRSA infection include diabetes mellitus, advanced age, immunocompromised state and prolonged hospitalization.[129] MRSA is a common pathogen to cause catheter-related complications in dialysis patients and is associated with significant patient morbidity and mortality.[130] In this context, MRSA is a frequent cause of exit-site infection, tunnel tract infection and peritonitis in PD patients. In HD patients, MRSA can cause HD catheter exit-site or tunnel tract infections, bacteremia or even infective endocarditis. The following section reviewed the treatment of MRSA infection among dialysis and advanced chronic kidney disease (CKD) patients. The strategies for screening and decolonization of MRSA will be elaborated in section F5.

Guideline statements

F.2.1.1. Parenteral vancomycin is the treatment of choice for MRSA infection in dialysis patients. (R)

F2.2.2. Daptomycin, linezolid, quinupristin-dalfopristin and tigecycline can be viable alternatives in patients who cannot tolerate vancomycin. (D)

Rationale

Parenteral vancomycin is an established treatment of MRSA infection in dialysis patients. Its clinical efficacy has been demonstrated in the treatment of MRSA exit-site infection, tunnel tract tunnel infection and peritonitis in PD patients.[42] Intravenous vancomycin (at a dose of 1 g every 5–7 days for total of at least 2 weeks) is a recommended treatment of MRSA exit-site or tunnel tract infection in PD patients.[42] Intraperitoneal (IP) vancomycin has been used with success for the treatment of MRSA peritonitis in PD patients. The ISPD guidelines recommended that IP vancomycin be administered for the treatment of PD-related peritonitis due to MRSA.[42] Vancomycin is also effective treatment for HD-catheter related infections including exit-site and CRBI.[131] Other options of MRSA treatment in dialysis patients include teicoplanin, daptomycin, linezolid, tigecycline and quinupristin-dalfopristin. Teicoplanin has the advantage of longer half-life and better tolerability than vancomycin. Daptomycin has been approved for the treatment of complicated MRSA skin infections and bacteremia (with or without endocarditis) in a dosage of 6 mg/kg per day.[132] The dosage should remain the same but the frequency should be reduced to every 48 h in stage 4 or 5 CKD patients.[133] Linezolid (at a dosage of 600 mg twice daily, IV or PO) has been approved for the treatment of MRSA skin infection as well as community- or hospital-acquired MRSA pneumonia.[134] No dosage modification is required for linezolid in dialysis patients but side effects such as thrombocytopenia and lactic acidosis need to be closely monitored.[134] Tigecycline shows good *in vitro* activity against the majority of MRSA strains and is an approved treatment for MRSA skin and intra-abdominal infections.[135,136] One advantage of tigecycline in CKD and dialysis patients is that it does not require dosage adjustment and has little concern regarding its timing of administration in relation to HD due to its poor dialyzability. There is lack of clinical data regarding the use of IP tigecycline for MRSA peritonitis although previous pharmacokinetics studies have demonstrated the stability of tigecycline in different concentrations of PD fluid.[137] Quinupristin-dalfopristin is approved for MRSA skin infections with no dosage adjustment in renal failure subjects but its data in dialysis patients is relatively limited.[133] Other novel treatments for MRSA infections include lipoglycopeptides dalbavancin, telavancin, and oritavancin as well as newer generation cephalosporins such as ceftobiprole and ceftaroline.[135,138,139] The data on these emerging therapies for MRSA, however, is still lacking among renal failure patients and further studies are required to demonstrate their efficacy in such clinical context. Furthermore, some of these agents are still not available in many local centres and hence limiting their clinical utility.

Limitations

There is a steady rise of minimal inhibitory concentration (MIC) for vancomycin over time in *S. aureus* strains.[132] Infections due to MRSA strains with an increased MIC for vancomycin (>1–2 μg/mL) confers escalated mortality risk.[140,141] Vancomycin intermediate *S. aureus* (VISA) are MRSA strains with MIC between 2 and 16 μg/mL and patients infected with VISA are at risk of treatment failure.[142]

Implementation issues

There is limited clinical experience with the use of alternative and novel agents other than vancomycin for MRSA infection in dialysis. Due to its established efficacy and relatively low cost, parenteral vancomycin remains the treatment of choice for MRSA infection in dialysis patients.

Audit measures

The incidence/prevalence and antibiotics susceptibility profile (including MIC) of MRSA infection in a renal unit should be periodically audited. These data will have implications on the screening/decolonization strategies of MRSA as well as the choice of treatment for MRSA infection within the dialysis unit.

F2.2 Vancomycin-resistant enterococcus

Introduction

VRE are strains of *Enterococcus* which showed resistance to vancomycin (defined as MIC ≥32 μg/mL). *E. faecium* and *E. faecalis* account for the majority of VRE isolates. VRE is an escalating threat to the health-care system and outbreaks have been reported in various hospital settings.[143] VRE infections are closely linked to unfavourable clinical outcomes and patient mortality is significantly higher than infections due to vancomycin-susceptible entercoccal isolates.[144]

Guideline statements

F2.2.1. Linezolid is the treatment of choice for VRE infection in renal failure patients. (R)

F2.2.2. Contact precautions, good hand hygiene practices single room isolation or cohorting (if single room is not available) are recommended for patients infected or colonized with VRE. (R)

F2.2.3. Active surveillance cultures can be considered during outbreak or in high-risk patients if the incidence or prevalence of VRE in the facility is not decreasing despite stringent implementation of routine infection control measures. (D)

F2.3.4. Eradication of VRE in patients colonized with VRE is not routinely performed and further investigation is required. (R)

Rationale

Linezolid is an approved treatment for VRE infections and is active against both vancomycin-resistant *E. faecalis* and *E. faecium*, and no dosage modification is required in dialysis patients.[145,146] Clinicians need to be aware of the potential side effects of myelosuppression (e.g. thrombocytopenia) and lactic acidosis with prolonged administration of linezolid. Alternative treatments for VRE infections include daptomycin and tigecycline, but their efficacy is less reliable in VRE bacteremia and higher doses might be warranted.[145,147,148] Quinupristin-dalfopristin can be an alternative for VRE treatment but its indication for endocarditis has been removed recently.[145] As the resistance profile of VRE can be quite variable, clinicians should closely liaise with the microbiologists regarding the optimal choice of antibiotics for VRE infections.

The primary route of VRE transmission is via the hands of health-care professionals, and thus hand hygiene is the most important and practical means of preventing spread of VRE within the hospital.[149] In this context, soap and water as well as alcohol-based hand rubs are both effective and duration of hand washing should be up to 30 s.[150] Contact precautions (i.e. wearing of gloves and gowns during the care of VRE patients) can significantly decrease the VRE acquisition rates.[151,152] Cohorting of VRE patients and/or staff who care for colonized patients can also aid to diminish VRE transmission.[153,154]

Surveillance cultures for VRE can be obtained from rectal or peri-rectal swabs or stool samples.[155] Active surveillance cultures in outbreaks or in high-risk patients can be considered if the incidence or prevalence of VRE in the facility is not decreasing despite stringent implementation of routine infection control measures.[149,156,157] There is currently no effective strategy to eradicate VRE colonization and the efforts to decolonize with oral non-absorbable antibiotics have been disappointing.[155,158]

Limitations

The data and choice for the treatment of VRE in CKD and dialysis patients remain relatively limited. There is current no effective ways to eradicate VRE carriage.

Implementation issues

Compliance to contact precautions and good hand hygiene practice can be difficult in dialysis units with high patient load and turnover. Furthermore, single room isolation or cohorting VRE patients with contact precautions will have significant resource and manpower implications to the unit.

F2.3 ESBL-producing gram-negative bacteria

Introduction

Extended spectrum beta-lactamase-producing Gram-negative bacteria (GNB) frequently cause infections (e.g. UTI, pneumonia or catheter-related infections) among renal failure patients. Infection due to ESBL-producing organisms is a growing problem in dialysis patients and is associated with increased patient mortality.[125,159,160]

Guideline statements

F2.3.1 Carbapenem, with appropriate dosage adjustment, is the treatment of choice for ESBL-producing GNB in renal failure patients. (R)

F2.3.2 Tigecycline can be an alternative treatment for ESBL-producing GNB in renal failure patients who have allergy to β-lactam antibiotics. (D)

Rationale

The use of carbapenem has established clinical benefits on patient survival and bacteriological clearance.[160–162] IP carbapenems have been used with success in PD-related peritonitis due to ESBL-producing organisms.[163,164] Tigecycline can be a viable alternative for the treatment of ESBL-producing organisms, especially in patients with allergy to β-lactam antibiotics.[165] Its relatively low and steady rate of drug resistance is another added merit.[166] Other advantage of tigecycline in CKD and dialysis patients is the little concern for dosage adjustment and the timing of administration in relation to HD.

Limitations

The rising incidence of ESBL-producing GNB is a growing concern in dialysis unit due to its limited therapeutic options and implications on health-care burden for isolation and prevention of transmission. The increased use of carbapenem also poses a risk of carbapenem-resistance.

Implementation issues

The restricted use of cephalosporins can be difficult among dialysis patients who have frequent infections and attendance to health-care services. Adherence to standard precautions with good hand hygiene practice using alcohol-based hand rub can help reduce transmission of ESBL-producing organisms, but can be difficult in dialysis with high patient load and turn-over.

Audit measures

The incidence and antibiotics susceptibility profile of ESBL-producing GNB should be regularly monitored and reviewed. These data should be reflected to the clinicians to facilitate a more scrutinized use of antibiotics (especially cephalosporins). The compliance to infection control practice during the care of patients infected or colonized with ESBL-GNB should also be audited.

F2.4 Multidrug-resistant *Acinetobacter baumannii*

Introduction

Acinetobacter baumannii (*A. baumannii*) has both intrinsic and extrinsic mechanisms to develop resistance to multiple commercially available antibiotics, and multidrug-resistant *A. baumannii* (MRAB) refers to strains which are resistant to all agents in four antibiotics classes (fluoroquinolones, aminoglycosides, cephalosporins, beta-lactam/beta-lactamase combinations).[167] Infection due to resistant strains of *A. baumannii* is associated with higher mortality and hospitalization costs as compared with infections due to susceptible strains.[168,169]

Guideline statements

F2.4.1 Polymyxins (B or E) are the treatment of choice for MRAB in renal failure patients. (R)

F2.4.2 Alternative options of MRAB treatment include minocycline and tigecycline in patients who are intolerant to polymyxins. (D)

F2.4.3. Transmission of MRAB can be reduced by early recognition of MRAB cases, aseptic handling of vascular catheters as well as adherence to hand hygiene and disinfection procedures. (R)

Rationale

There are limited options for the treatment of MRAB and commonly used agents include polymyxins (B or E), minocyclines and tigecycline. Polymyxin B and E (colistin) appeared to have the most extensive clinical data for the treatment of MRAB although the randomized trials addressing their efficacy in MRAB is lacking. The clinical efficacy of polymyxin E had been demonstrated in pneumonia, bacteremia and meningitis caused by MRAB.[170–172] Successful treatment of PD-related peritonitis due to MRAB with IP polymyxin B and ampicillin-sulbactam had also been reported.[173] Clinicians should be aware of the potential nephrotoxicity and neurotoxicity (paraesthesia) when polymyxins are used in CKD or dialysis patients, and appropriate dosage adjustment has to be exercised.[174] Tigecycline have also shown activity against MRAB but there is limited data regarding its use for the treatment of MRAB in renal failure patients.[175,176] Moreover, the use of tigecycline in MRAB was associated with increased mortality when compared with other treatments and thus should only be considered when no other options are available.[177]

Active surveillance, contact isolation, compliance with hand hygiene and aseptic care of vascular catheters are essential measures to control MRAB transmission.[178,179] MRAB remains largely susceptible to disinfectant and antiseptics, and reports of disinfection failure are likely related to failure to follow cleaning procedures rather than emergence of resistance.[180]

Limitations

The data regarding the treatment of MRAB are primarily derived from treatment of other infections in the general population. There is also paucity of data on combination therapy of MRAB, especially in renal failure patients.

Implementation issues

Therapeutic choices for MRAB infections are limited. The need for isolation, prolonged treatment and hospitalization will impose substantial burden to a dialysis unit.

Audit measures

The incidence and antibiotics susceptibility pattern of MRAB in a dialysis unit should be regularly audited and reflected to the clinicians. These data will help assess the effectiveness of the infection-control measures and guide the use of antibiotics in a nephrology unit.

F2.5 *Clostridium difficile*

Introduction

Clostridium difficile (*C. difficile*) is the most common cause of transmissible nosocomial infection in health-care facilities.[181] Renal failure patients are of escalated risk of *C. difficile* infection and hospital-associated morbidity and mortality.[182]

Guideline statements

F2.5.1. The inciting antibiotics should be discontinued as possible. (R)

F2.5.2. Both oral metronidazole and oral vancomycin are effective treatment for mild *C. difficile* infection in renal failure patients. (R)

F2.5.3. Oral vancomycin is the preferred treatment in renal failure patients who suffered from severe *C. difficile* infection. (R)

F2.5.4. Contact precautions and good hand hygiene practices are recommended to prevent *C. difficile* transmission in a dialysis unit. Soap and water is preferred to alcohol-based disinfectant for hand sanitization during an outbreak situation. (R)

Rationale

One key initial step in the management of *C. difficile* infection is the discontinuation of inciting antibiotics.[181,183] Several randomized trials have demonstrated that oral metronidazole and oral vancomycin are equally effective for the treatment of non-severe *C. difficile* infection.[184–186] Oral metronidazole is associated with very low treatment costs, but its use is also associated with higher recurrence rates. Due to its non-absorption in the gastrointestinal tract, oral vancomycin can achieve high local concentration and thus should be used for severe *C. difficile* infection.[181,183] In one prospective randomized double-blind clinical trial, oral vancomycin was shown to be superior to oral metronidazole for the treatment of severe *C. difficile* infection (cure rate 97 *vs* 76%).[184] Contact precautions and hand sanitization (before and after patient care) should be exercised in patients with suspected or confirmed *C. difficile* infection.[181] Soap and water is more preferred than alcohol-based disinfectants to achieve hand hygiene as *C. difficile* spores are resistant to alcohol.[181]

Limitations

Being an anaerobic organism, the culture of *C. difficile* in stool samples can be difficult and the diagnosis often requires the identification of *C. difficile* toxin.

Implementation issues

The discontinuation of inciting antibiotics can be difficult as many dialysis patients require these antibiotics for other concomitant infections and very often the choice of alternative antibiotics is limited. Adherence to contact precautions and hand sanitization can be problematic in nephrology units with high patient load and turnover.

Audit measures

The incidence and treatment outcomes of *C. difficile* infections should be regularly audited. These data will help review current infection control measures in a dialysis facility and guide the choice of antibiotics for the treatment of *C. difficile*.

F3 Other infections (e.g. MDR-TB)

Introduction

While there is established and effective treatment for usual TB infections, there is growing drug resistance to commonly used anti-TB agents.[187] Multidrug-resistant TB is defined as isolates of *M. tuberculosis* that are resistant to at least isoniazid and rifampicin, and has presented significant challenge in patient management due to the limited choice of therapeutic agents and associated treatment toxicities.

Guideline statements

F3.1. Treatment regimen for MDR-TB infection in renal failure patients should comprise fluoroquinolones and injectable aminoglycosides. Aminoglycoside should be used with caution in CKD patients and dialysis patients who still have considerable residual renal function. (R)

F3.2. Other possible options for the treatment of MDR-TB in this locality include linezolid, ethionamide and cycloserine. (D)

F3.3. The infectivity of dialysis patients with suspected or confirmed MDR-TB should be determined by their clinical status, sputum smear and radiographic findings, and appropriate infection control measures should be applied accordingly. (R)

Rationale

A treatment regimen for MDR-TB consists of multiple second-line anti-TB agents which usually includes fluoroquinolones and injectable aminoglycosides.[188] One should be cautious in administering these agents in CKD patients and dialysis patients who still have considerable residual renal function. Other second-line agents include linezolid, ethionamide, cycloserine.[189,190]

The infection precautions of MDR-TB are similar to that of drug-susceptible TB. The infectivity of a MDR-TB patient should be weighed with regarding to their clinical status and sputum smear results.[191] A patient is considered infectious if: (i) they are undergoing cough-inducing procedures; (ii) they have positive sputum smear results for acid fast bacilli; (iii) they have cavitary lesions evident on chest radiography; (iv) they are not receiving adequate anti-TB treatment or show poor clinical response to therapy. Airborne precautions should be strictly exercised in MDR-TB patients with infectivity. In this context, patients should be cared in an isolation ward and dialysis should be performed in areas with appropriate airborne precaution facilities.

Limitations

The data regarding treatment of MDR-TB in dialysis population remains relatively limited. The data concerning novel agents such as bedaquiline and delamanid are lacking in CKD and dialysis patients, and the availability of these agents remain an issue.

Implementation issues

Treatment of MDR-TB remains difficult in CKD and dialysis patients due to limited therapeutic options and increased drug intolerance. The exaggerated side effects in renal

failure patients can contribute to poor drug compliance and frequent modification of drug regimen, and hence increased risk of treatment failure and drug resistance. The need for isolation facilities during patient care and dialysis also impose substantial resource burden to a dialysis unit.

Audit measures

The incidence, sites of involvement and susceptibility pattern of TB infection in the dialysis unit should be periodically monitored. These data will help refine current infection control policy for TB in a dialysis unit.

F4 Management of febrile patients in the dialysis unit

Introduction

Fever in a dialysis patient is frequently related to infections, although other causes such as drug fever, allergic response to components of the HD circuit, deep vein thrombosis, autoimmune diseases or tumour fever are also possible differential diagnoses.[192] A systemic and established protocol of febrile patients in a dialysis unit can improve overall patient outcomes and dialysis unit performance.

Guideline statements

F.4.1 Initially investigations for febrile patients in a dialysis unit should include proper history taking and physical examination, chest radiography and other appropriate microbiological studies including peripheral blood cultures. Clinical samples relevant to the mode of dialysis (e.g. peritoneal fluid cell count and culture in PD patients, blood culture from central catheter in HD patients) should be obtained. (R)

F4.2 Empirical antibiotics should take into consideration the presenting clinical features, underlying medical diseases, spectrum of coverage and previous culture and susceptibility pattern of organisms. (R)

Rationale

Infection remains the most common cause of fever in dialysis patients. The investigation of febrile patients in a dialysis unit should begin with proper history taking and physical examination.[192] The history should include the onset and time course of fever, associated symptoms, travel and contact history, as well as zoonotic and occupational exposures. Special attention should be directed to the dialysis access such as the PD or HD catheter exit sites and AV fistula/graft.[193,194] Initial laboratory investigations include complete blood picture, liver and renal biochemistry, peripheral blood culture, chest radiography and other appropriate microbiological studies (e.g. sputum culture, urine culture, nasopharyngeal aspirate and wound swab cultures). Clinical samples relevant to the patient's mode of dialysis should also be obtained (e.g. peritoneal fluid cell count and culture in PD patients, blood culture from central catheter in HD patients). Serum IgE levels can also be checked if allergy to components of the HD circuit is suspected. Empirical antibiotics should be promptly initiated after appropriate microbiological samples have been obtained. The choice of empirical antibiotics should take into consideration the presenting clinical features, underlying medical diseases, spectrum of coverage, as well as the previous culture and susceptibility pattern of organisms isolated from the patient. For instance, dialysis patients who received immunosuppressive treatments or suffered from neutropenia or septicemia should receive more broad-spectrum IV antibiotics. Unusual pathogens such as atypical organisms, mycobacteria, fungi or MDRO should be considered if patients respond poorly to first-line antibiotics. Removal of PD or HD catheter should be warranted in patients with profound sepsis or poor response to medical therapy.[42] Alternative causes of fever such as drug fever, autoimmune diseases, malignancy or allergy to the components in the HD circuit should also be properly excluded.[192,195–197]

Limitations

There is currently no established guideline on the workup and treatment of febrile patients in dialysis units. The investigation and empirical treatment of febrile patients depends on the clinical presentation, underlying medical diseases, previous culture and susceptibility profiles and local clinicians' experience.

Implementation issues

The high patient variability and the difference in practices among clinicians have contributed to the difficulty in implementation of standard protocols for the management of febrile patients in a dialysis unit.

Audit measures

The incidence/prevalence, type of organism isolated (including susceptibility patterns) and clinical outcomes of febrile patients in a dialysis unit should be regularly reviewed. The data should help refine the current protocol for the management of febrile patients in a dialysis unit.

F5 Management of patients with *staphylococcus aureus* colonization

Introduction

S. aureus is one of the most common pathogens to cause infections in dialysis patients. In this context, both methicillin-sensitive *S. aureus* (MSSA) or MRSA are frequent organisms to cause exit-site and tunnel tract infections as well as peritonitis in PD patients. In HD patients, MSSA and MRSA can cause HD catheter exit-site or tunnel tract infections, bacteremia or even infective endocarditis. Against these backgrounds, the majority of studies have focused on the screening and decolonization of MRSA in dialysis patients with an attempt to reduce MRSA infections and health-care burdens.

F5.1 Screening

Guideline statements

F5.1.1. Active surveillance for MRSA should be considered when there is an established outbreak. (R)

Rationale

The primary objective of *S. aureus* screening programs is to identify at risk patients and perform carrier decolonization to reduce individual risk of infection. Previous studies have addressed the effectiveness of screening and decolonization as part of broader policies to limit the spread of MRSA.[125,149,198–201] Most of these studies employed a quasi-experimental design, with institution of several preventive measures at the same time. While these studies have suggested the effectiveness of screening/decolonization strategies, the positive results might be confounded by publication bias. Recent advances in PCR-based screening have prompted larger and better-designed studies to address this issue and have generated some conflicting results.[199–201] Based on these data, the practice of routine screening for MRSA in dialysis patients remained controversial. However, active surveillance should be undertaken when there is an established outbreak.[126,127]

Limitations

The epidemiology of *S. aureus*, especially MRSA is complex and poorly understood. Screening and decolonization strategies are often implemented as part of a broader infection control program, and thus the individual benefits of screening, contact precaution and decolonization remained unclear.

Implementation issues

Regular surveillance of *S. aureus* carriage has resource and manpower implications. The extent and optimal method of screening remain controversial.

Audit measures

The incidence and prevalence of MRSA carriage and infection should be regularly monitored. A changing incidence/prevalence of MRSA infection should prompt review of the current MRSA screening policy and infection control measures.

F5.2 Decolonization of MRSA carriage

Guideline statements

F5.2.1. Decolonization of MRSA in dialysis patients can be achieved via topical or intra-nasal application of mupirocin alone or in combination with systemic antimicrobial plus an antimicrobial-containing bath. (R)

F5.2.2. Asymptomatic health-care providers who are not epidemiologically linked to MRSA transmission do not require decolonization. (R)

F.5.2.3. Decolonization should be considered in health-care providers who are implicated in MRSA transmission and rendered culture negative before returning to patient care. (D)

Rationale

Pooled data from meta-analysis and multicentre randomized controlled trials have demonstrated the benefits of *S. aureus* (MSSA and MRSA) decolonization in high-risk patients.[35,202] The use of topical combined with systemic decolonization appeared to have higher success rates than topical decolonization alone.[203] Possible decolonization regimens include intra-nasal mupirocin alone or in combination with oral antibiotics (e.g. rifampin in combination with cotrimoxazole or ciprofloxacin or doxycycline) plus the use of an antimicrobial (e.g. chlorhexidine gluconate or povidone iodine) for bathing.[203–205] Decolonization should be considered in health-care providers who are implicated in MRSA transmission and be rendered culture-negative before returning to patient care. However, asymptomatic health-care providers who have not been linked epidemiologically to MRSA transmission do not require decolonization.[126]

Limitations

A successful decolonization program also depends on appropriate screening strategy. The attempts to decolonize MRSA carriers can be limited by recolonization and emergence of resistance to mupirocin or other antimicrobials.[205–207] Furthermore, follow-up surveillance cultures are required to ensure clearance in patients who have received eradication therapy.

Implementation issues

Routine surveillance and decolonization as well as follow-up cultures can impose significant resource and manpower burden to a renal unit.

Audit measures

The effect of the surveillance and decolonization program in a dialysis unit should be periodically reviewed to decide whether further change in policy is needed.

G OUTBREAK INVESTIGATION

G1 Commonly reported outbreaks in renal units and common sources

1. **HBV**: staff carrier, poor infection control, lack of patient and machine segregation, shared multi-dose IV drugs;
2. **HCV**: Ditto;
3. **VRE**: poor infection control, hands of health care worker (HCW) to skin and wounds of patients;
4. **MRSA**: poor infection control, hands of HCW to skin and wounds of patients;
5. **Non-glucose-fermenters** (*Burkholderia* spp, *Ralstonia* spp, *Pseudomonas aeruginosa* and spp, *Stenotrophomonas* spp): bacteraemia due to contaminated water system;
6. **Non-tuberculous mycobacteria** (*Mycobacterium abscessus* and *M. chelonae*): contaminated water system;

7. ***Klebsiella pneumoniae* or *Klebsiella oxytoca* (carbapenemase producing)**: poor disinfection of reprocessed dialyzer; failure of HCW to change gloves between patients;
8. ***Pneumocystis jirovecii***: renal transplant patients not on trimethoprim-sulfamethoxazole prophylaxis;
9. **Nocardia, Aspergillus and other mold infections** in renal transplant recipients: hospital renovation or building work dust;
10. ***Listeria monocytogenes*** in renal transplant patients: unboiled food items;
11. **Tuberculosis**: failure to isolate cases of open TB admitted in the same unit;
12. **Respiratory viruses** (influenza, parainfluenzavirus, respiratory syncytial virus, adenovirus, metapneumovirus, coronaviruses, rhinovirus, enterovirus): failure to isolate the index case in the same unit and poor infection control practice; poor influenza vaccination uptake in patients and HCW in the same unit;
13. **Endotoxin**: water contamination
14. **Chemical contamination** outbreaks of intoxoication (Aluminium seizure/dementia, Chloramine and copper leading to hemolysis, Fluoride and formaldehyde fatality, hydrogen peroxide and anaemia, nitrate leading to methaemoglobinemia, sodium azide and severe hypotension, sulphate leading to fever and gastrointestinal upsets.

G2 Hospital outbreak

An outbreak is defined as an increase in occurrence of an infection above the background rate. It may be one episode of a rare occurrence or many episodes of a common occurrence. In the health-care setting, a hospital outbreak can be practically defined as three or more patients acquiring epidemiologically important agents after 48 h of hospitalization in the same ward. Epidemiologically important agents were classified into four categories: (i) respiratory viruses (influenza A virus, influenza B virus, respiratory syncytial virus, human metapneumovirus, parainfluenza virus, adenovirus and rhinovirus), (ii) gastrointestinal pathogens (norovirus, rotavirus, Clostridium difficile), (iii) MDRO including vancomycin-resistant enterococci, carbapenemase-producing Enterobacteriaceae, multidrug resistant *Acinetobacter baumannii*. Hospital infection control team conducted surveillance, which is an ongoing, systematic collection, analysis and distribution of information regarding the occurrence of an infection in defined populations, to determine an occurrence of outbreak. In addition, frontline health-care workers can inform infection control team for clustering of cases in the clinical units.

G3 How to investigate an outbreak

All health-care workers must be committed to the investigation and implementation of control measures. The steps of carrying out an outbreak investigation are as follows.

G3.1 Case definition

To develop a working case definition based on the known facts of the outbreak. The working case definition must be able to include confirmed and possible cases within a defined time and place. Occasionally, the case definition may need to be refined as the outbreak investigation proceeds and more information is available.

G3.2 Case finding

Once a working case definition is developed, additional case finding can be conducted.

G3.3 Epidemic curve

To describe the outbreak over time, one can plot the number of cases (Y-axis) against time (X-axis) and identify the possible source and mode of transmission of the outbreak. For example, a point source outbreak such as gastrointestinal viral infection usually gives a high peak, followed by continued cases of illness. The epidemic curve of an outbreak due to lapse in infection control practices or contaminated patient equipment usually be spread over a long period, as illustrated in the outbreaks of vancomycin-resistant enterococci, carbapenemase-producing Enterobacteriaceae, multidrug-resistant *Acinetobacter baumannii* in the hospital.

G3.4 Line listing

To obtain the patient demographic and clinical information, one can design a questionnaire for data collection or reviewing medical record. Important such as age, sex, underlying diseases, invasive procedures, presence of catheters, caring clinicians and nurses, exposure to other health-care workers, use of medications and IV fluid. After reviewing the records, one should develop a table containing the data of the patients.

G3.5 Formulation of a hypothesis

Once the epidemic curve and line listing are performed, hypotheses about the possible source of infection and how the infection is transmitted can be generated.

G3.6 Case–control study

To understand the potential risks contributing to the outbreak, case–control analysis can be performed to complete the epidemiological investigation. For example, if 30 affected patients or health-care workers are enrolled, a proportional number (e.g. 30, 60) of unaffected members of the at-risk population should be enrolled as control subjects. Comparison of the exposure to potential risk factors in the patients with that in the control group can be performed by univariate analysis. Since hospital outbreaks usually involve a small number of cases, stratifying the data and multivariate analysis are usually not possible.

G3.7 Microbiological analysis

To confirm the clonal relationship between the outbreak strains, genetic relatedness can be assessed by pulse-field gel electrophoresis, multilocus sequence typing, and recently whole-genome sequencing.

H ANTIMICROBIAL STEWARDSHIP

H1 Introduction

Unnecessary or inappropriate use of antimicrobial agents is the most important cause for the emergence and dissemination MDRO. This has been well demonstrated by the initial emergence of vancomycin-resistant staphylococci, vancomycin-resistant enterococci, extended spectrum beta-lactamase producing- and carbapenemase producing-enterobacteriaceae in renal dialysis patients. The onset of invasive infection by these multidrug-resistant bacteria often starts as asymptomatic colonization of skin and mucosa of renal patients, which is followed by invasive disease at Tenckhoff or HD indwelling vascular devices. Thirty to forty per cent of chronic HD patients receive at least one dose of antimicrobials as outpatient over a 1-year period. In many public hospitals, up to 30% of these antibiotics are prescribed inappropriately according to the improved protection against CMV in transplantation (IMPACT) guidelines.[208–211]

During our daily antibiotic auditing meeting, we find that the most common mistakes include

1. Failure to de-escalate to a more narrow-spectrum antibiotic;
2. The clinical criteria for the diagnosis of an infection such as skin and soft tissue infections are not satisfied;
3. The choice and duration for surgical prophylaxis for vascular-access-related procedures are not following the IMPACT guideline;
4. The most commonly abused antibiotics are vancomycin, and third- or fourth-generation cephalosporins.

Antimicrobial stewardship program is therefore necessary for ensuring:

1. Optimal selection of dose and duration of antimicrobial therapy;
2. Best clinical outcome for the treatment or prevention of infection;
3. Fewest toxic effects and the lowest risk for subsequent resistance.

Antimicrobials have been termed 'societal' drugs because antimicrobial resistance can develop during antimicrobial therapy, any resistant organism that emerges can be spread to persons who have never been exposed to the antimicrobial. Thus, the use and misuse of these resources have 'societal consequences'.

H2 Choice of antimicrobial stewardship strategies

Strategy	Procedure	Personnel	Advantages	Disadvantages
Education guidelines	Creation of guidelines for antimicrobial use.	Antimicrobial committee to create guidelines.	May alter behavioural patterns.	Passive education likely ineffective.
	Group or individual education of clinicians by educators.	Educators (clinical microbiologist, infectious disease physicians).	Avoids loss of prescriber autonomy.	
Formulary restriction	Restrict dispensing of targeted antimicrobials to approved indications.	Antimicrobial committee to create guidelines.	Most direct control over antimicrobial use.	Perceived loss of autonomy for prescribers.
		Approval personnel (clinical microbiologist, infectious disease physicians).	Individual educational opportunities.	Need for all-hours consultant availability.
Review and feedback	Daily review of targeted antimicrobials for appropriateness.	Antimicrobial committee to create guidelines.	Avoids loss of autonomy for prescribers.	Compliance with recommendations voluntary.
	Contact prescribers with recommendations for alternative therapy.	Review personnel (usually clinical pharmacist, infection control nurse (ICN), in Hong Kong).	Individual educational opportunities.	
Computer assistance	Use of information technology to implement previous strategies.	Antimicrobial committee to create rules for computer systems.	Provides patient-specific data where most likely to impact (point of care).	Significant time and resource investment to implement sophisticated systems.
	Expert systems provide patient-specific recommendations at point of care (order entry).	Personnel for approval or review (physicians, pharmacists), computer programmers.	Facilitates other strategies.	
Antimicrobial cycling	Scheduled rotation of antimicrobials used in hospital or unit (e.g. intensive care unit).	Antimicrobial committee to create cycling protocol; personnel to oversee adherence (pharmacist, physicians).	May reduce resistance by changing selective pressure.	Difficult to ensure adherence to cycling protocol Theoretical concerns about effectiveness.

The antimicrobial stewardship program can be functionally classified as:

1. Back-end program (prospective audit with intervention and feedback).
   Antimicrobial use is reviewed after antimicrobial therapy has been initiated and recommendations are made as to their appropriateness in terms of selection, dose, route and duration. For instance, 'big gun' antibiotics (imipenem, meropenem, ertapenem, cefepime, ceftazidime, cefoperazone-sulbactam and piperacillin-tazobactam, glycopeptides (vancomycin, teicoplanin)), tigecycline in Queen Mary Hospital.
2. Front-end programs (prior authorization).
   Antimicrobials are made accessible only through an approval process.

H3 Potential barriers to reaching the strategic goals

Barrier	Counter-measures and improvement strategies
Ownership and accountability	
Lack of ownership and accountability for recognizing and reporting trend.	Designate responsibility and accountability for the process.
Failure to integrate work of laboratory, infection-control, medical, nursing, and care-unit staff.	Set up a multidisciplinary team to develop a collaborative system and monitor results.
Staff knowledge and practice	
Lack of time for the laboratory and/or infection-control staff to generate and analyze data.	Ensure adequacy of laboratory and infection-control staffing and prioritize activities of staff so that data can be generated and analyzed.
Lack of time for health-care providers to examine and discuss data, and inconsistent or erroneous interpretation of data by staff.	Report data in an easy-to-read or interpret format and, when appropriate, include data interpretation in the report.
Physician attitudes	
Lack of trust in the hospital administration.	Use a data-driven approach to cultivate trust, for example, communicate regularly with physicians about trends in antimicrobial usage, cost and resistance, feedback to individual physicians about their performance results
Expertise	
Lack of expertise in biostatistics (e.g. presenting trends and analyzing data).	Ensure availability of consultants, especially when designing analytical strategy and interpreting trend data.

H4 Methods to implement antimicrobial control (back-end programme)

1. Provision of written hospital guidelines.
2. IMPACT guideline is available through: http://www.chp.gov.hk/files/pdf/reducing_bacterial_resistance_with_impact.pdf or App in both iPhone and Android system.
3. Educational efforts aimed at changing prescribing practices of physicians.
4. Providing consultation from clinical microbiologist or infectious diseases specialist.
5. Restriction of hospital formulary through the Drugs and Therapeutics Committee.
6. Utilization review with guidelines for rational and appropriate usage.
7. Ongoing monitoring and analysis of antimicrobial usage.
8. Ongoing surveillance of antimicrobial susceptibility.
9. Monitoring adherence to advice on choice of antimicrobial agents.
10. Feedback to physicians.

H5 Future challenge of antimicrobial stewardship programs in Hong Kong

1. Increasing trend of antimicrobial resistant organisms – emergency of CRE, nosocomial outbreaks of VRE, and increasing prevalence of MRSA in long-term care facilities.
2. Requiring a comprehensive overview of all broad-spectrum antimicrobials agents with epidemiological potential to select antimicrobial resistance, instead of only focusing on a group of selected 'Big gun' antibiotics.
3. Requiring additional resources in terms of manpower and information technology support to enhance the efficiency of workflow.

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