CRITICAL CARE MICROBIOLOGY 2- MICROBIOLOGY CHALLENGES IN CRITICAL CARE
ANAESTHESIA TUTORIAL OF THE WEEK 182

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation.

1. Which of the following statements concerning Clostridium Difficile is correct?
    a. It is a gram-negative rod
    b. It acts via 3 toxins; Van A, B and C
    c. It is not susceptible to alcohol gels
    d. First line treatment is with iv metronidazole

2. Concerning Acinetobacter Baumannii, which of the following is true?
    a. It is a gram negative bacillus
    b. It prefers wet to dry conditions
    c. It may be panresistant
    d. Outbreak control may require unit closure

3. MRSA
    a. Is a gram positive aerobic rod
    b. Is associated with excess mortality in critical care patients
    c. May be assumed to be eradicated after 3 clear swabs for infection control purposes
    d. Eradication of carriage is with mupirocin nasal ointment and octenisan baths

4. Extended-spectrum beta lactamase producers
    a. Were first described in association with Pseudomonas spp.
    b. Remain sensitive to Tazocin
    c. Remain sensitive to Meropenem
    d. Are common in urology patients

INTRODUCTION

This is the second part of the series on critical care microbiology and focuses on common organisms encountered in intensive care practice, in particular those which are common nosocomial pathogens and are problematic by virtue of resistance.

GRAM POSITIVE ORGANISMS

MRSA (Methicillin-resistant Staph Aureus)

Description

This most important nosocomial pathogen can be thought of pragmatically as "FRSA" in recognition of the fact that flucloxacillin, not the superseded methicillin, resistance defines the organism in hospital practice.

Staph Aureus' resistance is carried on the MEC-A gene, which is carried initially by a transposon, or mobile genetic element, but integrates into the bacterial chromosome and codes for a low-affinity penicillin binding protein (2A) in the cell wall. This confers resistance to all beta-lactam antibiotics.

Infection

MRSA may present as asymptomatic carriage in anterior nares, axilla, perineum, umbilicus in infants, hospital or ICU-acquired as wound infection, bacteraemia or ventilator-associated pneumonia (VAP). Risk factors for carriage are well-described and include nursing or residential home residence, previous hospitalisation, indwelling catheters, surgical wounds, burns, critical care stay and importantly previous MRSA carriage or infection even in the distant past-"once MRSA, always MRSA". It is particularly important when bacteraemias occur or a native or prosthetic valve, indwelling device such as a central line, graft or mesh becomes infected as staphylococcus is difficult to eradicate using antibiotics alone in these areas and radical surgery may be needed. Concern is growing over Vancomycin-intermediate and –resistant Staph Aureus, sometimes summarised as Glycopeptide resistant SA or GISA.

Sporadically in the UK, but prone to epidemics in the USA, is a virulent strain of community-acquired MRSA (CA-MRSA) producing a multitude of virulence factors not found in hospital-acquired MRSA. One of these is the Panton-Valentine leukocidin (PVL). This causes community-acquired infection in previously healthy young people and presents as necrotising skin and soft tissue infections or necrotising pneumonia.The latter carries a high mortality (in excess of 60%).

Prevention and Infection control

Prevention centres on scrupulous antibiotic husbandry, appropriate antibiotic prophylaxis for surgical procedures, barrier precautions including isolating carriers is , rapid screening of patients especially in the perioperative setting, robust tracking of "old" MRSA cases in hospital casenotes and laboratory systems. A common and easily avoided mistake is the use of penicillins or cephalosporins to treat e.g. skin infections in patients who have previously had MRSA- this is a significant risk factor for MRSA bacteraemia.

Treatment

Treatment of nasal carriage is with mupirocin 2% ointment to the anterior nares tds for 5 days and Chlorhexidine or Octenisan top to toe bath or shower washes. A patient is considered "clear" for the purpose of isolation when 3 clear swabs hahve been obtained, although the caveat above pertains. Staff who are carriers may need to undergo the same treatment in the event of outbreaks, though recolonisation is common.

Despite its devastasting consequences, drug design for MRSA and other gram-positive infections is active, with several newer agents on the horizon. Aside from the glycopeptides, agents include linezolid, daptomycin, quinopristin-dalfopristin and tigecycline. Linezolid and clindamycin plus or minus intravenous immunoglobulin (IVIG) and rifampicin are used for PVL-producing MRSA if toxic-shock syndrome-like features are present.

Clostridium Difficile

Description

It is a gram positive anaerobic rod which sporulates and is commonly found in the human colon.

Infection

This challenging organism can cause a range of presentations ranging from asymptomatic carriage through clostridium difficile-associated diarrhoea, pseudomembranous colitis and toxic megacolon C Difficile exerts effect through the production of 2 toxins: Toxin A, an enterotoxin, causes fluid sequestration into bowel, whereas toxin B is cytotoxic. A new hypervirulent form known as BNP1/NAP1/027 which expresses far greater quantities of Toxin A and B as well as binary toxin has been described since 2000 and caused outbreaks in North America and Europe. Outbreaks are common especially on intensive care units and elderly care wards. At risk individuals are the elderly, immunosuppressed and those with a recent course of broad spectrum antibiotics, especially cephalosporins, flouroquinolones, ampicillin and clindamycin. Proton pump inhibitors may suppress a protective effect of gastric acid. The characteristic diarrhoea is foul, offensive and its severity can be graded with the Bristol stool chart or similar.

Diagnosis

The diagnosis of C.difficile has traditionally been made in a susceptible patient by stool assay of Toxin B. Newer ELISA tests detect both toxins. Colonoscopy and biopsy detects characteristic pseudomembranes and organisms, whereas proctoscopy alone may miss lesions. CT is recommended for cases where severe features are present, or where the diagnosis is difficult (some cases of severe disease do not have diarrhoea but ileus and distension).

Prevention and Infection control

The spores are resisitant to alcohol hand gels and present particular problems for environmental decontamination, as one bout of diarrhoea can cause spores to remain present in the envoronment and on on fomites for many months. Patients with a new diagnosis should be isolated, perferably in a single rooom with its own washbasin and toilet, or cohorted in an outbreak. Hand washing with soap, gloves and barrier precautions for staff and visitors are essential to avoid horizontal trasnsmission and disinfection of bedspaces and equipment with chlorine-containing antiseptics is required at least daily after diagnosis and after every toilet use. These principles are usefully memorised using the SIGHT (Suspect, Isolate, Gloves and aprons, Handwashing and Test) algorithm.

Prevention of infection is through good antibiotic stewardship and restriction of proton pump inhibitors (H2 blockers do not appear to be a risk factor). Restoring colonic flora involves enteral supplementation with live culture yoghurts containing Lactobacillus and may prevent overgrowth with C Difficile. A more radical and unpalatable solution recently described is the enteral infusion of emulsified faeces! IV immunoglobulin has been trialled with promising results.

Treatment

Antibiotic strategies are based on the principle of enteral administration of non-absorbable antibiotics. Metronidazole is generally regarded as a first line antibiotic, with vancomycin as second line. In those in whom enteral absorption is not possible, intravenous metronidazole (but not vancomycin) can be considered, and rectal administration of vancomycin has been used. Vancomycin is preferred in pregnancy and peripartum due to the teratogenicity of metronidazole.

For those who have fulminant colitis, peritonoitis, ileus or toxic megacolon, total- or subtotal-colectomy may be life-saving. Hemicolectomy tends to be avoided due to risk of residual or relapsing disease.The outlook for patients who undergo this surgery is poor, however, especially if multiple organ dysfunction is present preoperatively and inotropic therapy preop is a strong predictor of death.

Vancomycin (Glycopeptide)-resistant enterococcus (V(G)RE)

Description

Enterococci species, chiefly E. faecalis and E. faecium are gram positive gamma-haemolytic cocci, formerly known as Group D streptococci. They are part of the normal flora of the human intestine, the female genital tract and urinary tract. They are intrinsically of low pathogenicity but high resistance to antibiotics. VRE arise from enterococcal populations in patients previously exposed to vancomycin, teicoplanin and aminoglycosides. At –risk patients are transplant recipients, the immunosuppressed, ICU patients and elderly, those with NG feed. The species distinction can be important, since E faecalis remains largely sensitive to amoxicillin, vancomycin and teicoplanin, while E. Faecium is resistant. Gut carriage can persist for months or even years.

At least 6 resistance genes have been described (Van A-F), with Van-A the most commonly encountered. These are associated with multidrug- not just vancomycin, resistance.

Infection

VRE colonisation is common and does not always proceed to infection, but VRE can cause the range of infections commonly caused by enterococci, ie diarrhoea, bacteraemia, wound, device- and urinary infection and rarely, endocarditis,

Prevention and Infection control

Restriction of use of vancomycin and glycopeptides, use of faecal management systems and meticulous horizontal precautions, together with isolation when there is diarrhoea or urinary incontinence can help to prevent spread. Environmental cleaning with chlorine and phenol based disinfectant should also be undertaken after diarrhoea or vacation of a cubicle.

Treatment

VRE infection can be treated with linezolid, tigecycline, quinopristin-dalfopristin and daptomycin. Permanent clearance is difficult to achieve, as gut carriage can persist for months to years.

GRAM-NEGATIVE ORGANISMS

Pseudomonas Aeruginosa

Description

Pseudomonas aeruginosa is a non-fermenting gram-negative bacillus which is saprophytic and widespread in moist environments.

Infection

Pseudomonas characteristically causes "late" (more than 72 hours) ventilator-associated pneumonia. At risk patients include the immunosuppressed and patients with CF. It is intrinsically of low pathogenicity, but because of its abilities, firstly, to acquire resistance easily, and secondly, to survive on fomites and in water, including sinks, taps, water baths and ventilator tubing, it has become a very important nosocomial organism. It is difficult to eradicate from the lungs, due to the fact that it tends to form microabscesses and cause necrosis of alveolar walls, and relapses in cases of ventilator – associated pneumonia (VAP) are common.

Treatment Options

Aminoglycosides, eg. Gentamicin. The nephro- and oto-toxicity of these agents is well described and intravenous administration must be carefully monitored with regular levels. Gentamicin penetrates porly into the chest and is unsuitable for monotherapy for VAP.

Antipseudomonal penicillins and β-lactamase inhibitor combinations e.g . Tazocin (piperacillin/tazobactam). The use of these agents is fraught with the potential for acquisition of resistance. This may be circumvented to some extent by the use of drug infusions.

In some units, carbapenems such as meropenem are used as monotherapy for pseudomonas (VAP). In UK practice, meropenem is generally a second or third line agent, due to fears over extended spectrum β-lactamase producing Enterobacteriaciae (ESBLs), for which it is sometimes the only effective agent. A newer carbapenem, doripenem, is one of the few new agents with robust anti-pseudomonal activity.

Monobactams (e.g. Aztreonam) can be used in cases of penicillin allergy.

Third generation (e.g. ceftazidime) and fourth generation cephalosporins (e.g. cefipime). These are relatively narrow-spectrum and are often combined with a second agent.

The Surviving Sepsis 2008 guidelines endorse "double-coverage" and longer duration of antimicrobial treatment for Pseudomonas.

Inhaled adjuncts: Older agents such as tobramycin and colistin have undergone a resurgence as inhaled therapy in recent years. The rationale is that their neuro- and nephro-toxicity is recuced by minimal systemic absorption, while maintaining high local concentrations. There is some evidence of mortality reduction by this approach

ESBL (Extended Spectrum Beta-lactamase) and AMP-C-producing Enterobacteraciae

Description

Extended spectrum beta-lactamases were first described in association with Klebsiella Pneumoniae but have since emerged as a problem with the entire range of coliforms or Enterobacteraciae

These enzymes, of which there are over 500 classes, are exchanged between coliforms (including enterobacter, citrobacter, klebsiella, E coli, and serratia) as well as sometimes to proteus and rarely to pseudomonas mainly by plasmids, small extranuclear circles of DNA which may encode for multiple resistance. The TEM and SHV variants are transmitted in this way. The newer CTX-M ESBL is a mutated chromosomal variant derived originally from Kluyvera species. ESBL resistance is not always immediately obvious in vitro-initial apparent susceptibility of an organism to penicillins, cephalosporins or aztreonam may be followed later by detection of resistance. It can therefore present a problem for laboratories. AMP-C is an inducible chromosomal cephalosporinase enzyme which can be selected out by antibiotic usage including penicillin-beta lactamase inhibitor combinations, but can also be transmitted by plasmids and can co-exist with ESBL.

At-risk groups are ICU patients, the neutropaenic or otherwise immunosuppressed, those having previous repeated antibiotic courses, indwelling catheters, or multiple urological procedures.

Infection

These organisms cause the range of infections common to coliforms: urosepsis, intraabdominal and wound sepsis, ventilator associated pneumonia, bacteraemia.

Prevention and Infection control

Although ESBL infection may be selected as a result of inappropriate initial antimicrobial therapy it can spread through horizontal transmission. Previously implicated mechanisms are via patients' faeces and skin contamination of staff, infected equipment e.g. bronchoscopes and ultrasound gel amongst others. Those affected for example with incontinence and ESBL urinary tract infection (UTI), open wounds or drains should be isolated although there are no firm UK guidelines on this and many units perform individual risk assessments. Staff and visitor handwashing and rigorous environmental cleaning are important to prevent spread. Screening by e.g rectal swabs of asymptomativc patients is generally reserved for outbreaks. It is unclear how long a patient with an ESBL-producing organism should be treated as "positive".

Treatment

Currently, the carbapenems are not hydrolysed by ESBLs and are the treatment of choice. Carbapenem resistance is rare but should constitute an infection control emergency.

Inhaled adjuncts such as tobramycon and colistin are also used in cases of VAP.

Nitrofurantoin may be used in uncomplicated UTI when the patient can take medication orally.

Tigecycline is active against ESBLs but gives rise to low blood levels and is not excreted in the urine, making it unsuitable for the treatment of septicaemia and UTIs.

Acinetobacter Baumannii

Acinetobacter baumanni is a gram negative coccobacillus which derives its name from the fact that it does not possess a flagellum and is hence non-motile (Gk. Akineto-). It is found in soil and water and can resist dessication for several weeks.

Infection

Acinetobacter is an opportunistic organism with intrinsically high resistance levels to many antibiotics and which acquires resistance through the entire gamut of possible mechanisms including production of aminoglycoside-modifying enzymes, ESBLs, and carbapenemases, as well as through changes in outer membrane proteins, penicillin binding proteins, and topoisomerases.

It causes wound infections, hospital-acquired pneumonia (often with a multilobar infiltrate, cavitation, effusions and fistula formation) as well as bacteraemia. Infection with carbapenem-resistant A Baumanii is associated with increased ICU mortality. Because it can remain active for several weeks in both wet and dry environments it readily contaminates fomites and environment and assumes importance in disaster and conflict situations, including the 2004 Asian tsunami. Acinetobacter can contaminate ventilator humidification equipment and circuits as well as surfaces and keyboards, etc. It has recently come to prominence among returning soldiers from the Iraq conflict, earning the nickname "Iraqibacter" where the infection may have been caused through soil or sand contamination of wounds as well as contamination of equipment in mobile field hospitals.

Prevention and Infection control

Eradication of A baumannii during an outbreak is notoriously difficult. Persistent positive cultures are commonplace and may entail temporary closure of a unit for disinfection of equipment and environment A Baumannii is still sensitive to most disinfectants. Identification of staff who are colonised may be necessary and skin disinfection of patients and staff with chlorhexidine or polymyxin has been necessary

Treatment

Acinetobacter is resistant to most antibiotic classes. Carbapenems may be effective as may colistin given parenterally and polymyxin B. Tigecycline has been used but resistance is emerging.

Stenotrophomonas Maltophilia

Description

This is an aerobic, non-fermenting gram-negative bacillus formerly classified as a pseudomonad, and subsequently as Xanthomonas Maltophilia. The colonies resemble Pseudomonas and are occasionally misidentified as such.

It is notable for its very high intrinsic resistance, including, importantly, to carbapenems as well as beta-lactams, quinolones.

Infection

It is a common environmental pathogen which has been isolated on a wide variety of medical equipment. It is a frequent coloniser which can cause infection, particularly VAP, when host defences are compromised or bypassed as in the case of ventilated patients. Distinguishing colonisation from infection is important.

Prevention and Infection control

Patients with Stenotrophomonas VAP may be nursed in a bay provided closed-circuit suction is used.

Treatment

This organism has conventionally been treated with Sulphamethoxazole-trimethoprim (SMP-T, Septrin™) but some isolates have recently displayed resistance. Rifampicin and timentin may synergise with Septrin. Tigecycline has in vitro activity but there is little clinical experience with this agent in S maltophilia infection.

SUMMARY –

- Resistant nosocomial organisms are difficult to eradicate completely in carriers: assume once positive, always positive.
- Antibiotic policies should discourage use of high risk agents such as 3rd generation cephalosporins.
- Infection control measures are vital to prevent outbreaks.
- Currently the antibiotic armamentarium is good for gram positive- but worryingly sparse for resistant gram-negative organisms for whom the carbapenems are often the last resort.
- C. Difficile is not susceptible to alcohol gels.
- Stenotrophomonas maltophilia is intrinsically resistant to carbapenems.

ANSWERS TO QUESTIONS

5. Which of the following statements concerning Clostridium Difficile is correct?
   a. F. It is a gram positive organism
   b. F. This is true of VRE. It acts via toxins; Van A, B and C
   c. T. This is an important property.
   d. F. Enteral metronidazole

6. Concerning Acinetobacter Baumannii, which of the following is true?
   a. F. it is a coccobacillus
   b. F. It is equally at home in wet or dry conditions
   c. T.
   d. T.

7. MRSA
   a. F. A gram-positive coccus commonly seen in "bunches of grapes"
   b. T.
   c. T. But these patients remain at risk of further colonisation and infection.
   d T.

8. Extended-spectrum beta lactamase producers
   a. F. Originally described with Klebsiella
   b. F. Coverage cannot be assumed and resistance can occur during treatment
   c. T. Generally.
   d. T.

WEBLINKS

HPA - Health Protection Agency Homepage - Protecting people, Preventing harm, Preparing for threats
British Society of Antimicrobial Chemotherapy

FURTHER READING

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