Surveillance of Multidrug Resistant Organisms in a Tertiary Care Hospital in Delhi, India

Chand Wattal*, Neeraj Goel, JK Oberoi, Reena Raveendran, S Datta, KJ Prasad

Abstract

Surveillance of multi drug resistant organisms in a health care setting is a necessity to have optimum treatment out come and less of treatment failures. Once any health care setting gets colonized with multi drug resistant organisms, it is very difficult to decontaminate the environment. On review of our data, for 12 months of year 2008 the prevalence of difficult to treat organisms with poor clinical outcome especially in ICUs have been identified. The need for surveillance, prescription auditing & computer assisted retrieval of data has been emphasized and discussed in detail with respect to various high quality samples like blood, urine, respiratory, pus and sterile body fluids. The prevalence of MRSA & VRE has been documented 30 to 40% and 10%, respectively. Over all prevalence of penicillin intermediate resistant Streptococcus pneumoniae was found to be 9.52%. ESBL, AmpC, and Carbapenemase producing organisms were found to be 40 to 60%, 70 to 80% & 2 to 80% respectively in various multi drug resistant organisms like E. coli, Klebsiella spp., Pseudomonas spp. and Acinetobacter spp. 8% Pseudomonas spp. were found to be resistant to colistin in ICU samples. Enteric organisms were found to have high level ciprofloxacin resistant in 21.6% isolates, while S. paratyphi A isolation increased over a period of time. Yeast fungi isolated from blood predominantly were non-candida albicans (84.8%).

Introduction

Antimicrobial resistance is a global problem that needs urgent action. Development of antimicrobial resistance is a phenomenon inevitably related to microbial evolution and antibiotic use. Resistance to ‘first-line’ drugs in the pathogens causing diseases especially in ICU varies from zero to almost 100% and in some instances, resistance to second and third-line agents is seriously threatened, compromising treatment outcomes. Added to these major killers is the significant global burden of geriatric population & nosocomial infections, caused by rogue bugs.

Initial antibiotic selection must account for a variety of host, microbiologic and pharmacological factors. Institution-specific data, such as susceptibility patterns and local antibiotic use need to be studied. Tailoring antimicrobial therapy based upon culture and sensitivity results wherever available will help reduce cost, decrease, the incidence of super-infections, and minimize the emergence of resistance & mortality.

Though this is the scenario world over, in our country we are especially vulnerable due to the overwhelmingly indiscriminate use and across the counter availability of antibiotics. Presently India lacks any local or national level antimicrobial surveillance program, to guide the stakeholders on actual prevalence of resistance. At Sir Ganga Ram Hospital (SGRH) we documented yearly antibiotic surveillance data to track the resistance which also helped in formulating the antibiotic policy at our hospital. This review article provides evidence for us to act. The prevalence of only difficult to treat organisms & their antibiogrammes has been discussed here. Ignoring to recognize & appropriately treat such organisms can change the outcome of therapy in such infections.

Samples for Surveillance

To make surveillance meaningful it is necessary to know the variety of infections that a health care facility is confronted with. There are enumerable numbers of samples that are collected from patients suspected of having a sepsis syndrome and all may not be revealing or representative of a trend or nosocomial infection. However, some of the samples drawn like blood, urine, respiratory samples, fluids from sterile body spaces and soft tissues are considered to provide reliable baseline infection rate (nosocomial infections) at any given health care facility. Therefore, it becomes mandatory to include data generated from such samples routinely when surveillance data is being compiled for developing presumptive antibiotic guidelines at any one given place. It is also necessary to know prevalence of organisms & resistance at a demographic zone, which should be referred to instead of the global data for development of local infection control guidelines (Fig1 & Fig.2). Thereby, it becomes imperative to collate antibiogrammes obtained from samples of patients suffering from bacterial sepsicaemia, urinary tract infection (UTI), ventilator associated pneumonia (VAP), soft tissue and surgical site infections. This would give information about nosocomial infections as well. Besides these monitoring of central venous lines as a source of central line related blood stream infections (CRBSI) is an important part of the surveillance program that can reliably detect nosocomial infections more so in ICU settings. To detect CRBSI the microbiology laboratories that have automated blood culture systems (BacT/Alert or BACTEC) can practice differential time to positivity (DTP) cultures. Quality control procedures must be in place that can assure reliability and reproducibility of the data. It is also essential that microbiology laboratories follow standard operative procedures that are internationally acceptable. Preferably, as followed by most of the microbiology laboratories world over, CLSI guidelines should be practiced as much as possible. There are some of the organisms that cannot be reliably tested using disc diffusion techniques e.g. Streptococcus pneumoniae where MIC testing is mandatory. Similarly, to know synergistic sensitivities to predict clinical outcome in enterococcus isolated from other than urine, it is necessary to incorporate relevant procedures to generate synergistic antibiogrammes. The storage qualities of reagents (Penicillin and β lactam group of antibiotic testing discs) and temperature monitoring of incubators is an essential exercise to ensure generation of reliable reports. Similarly, routine detection of vancomycin resistant enterococcus (VRE), methicillin resistant S. aureus (MRSA) or extended spectrum β lactamases (ESBL) / AmpC / Carbapenemase producing

*Department of Clinical Microbiology, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India.
Methicillin-resistant S. aureus (MRSA)

MRSA was first identified only a year after the introduction of methicillin, a semi synthetic penicillin. MRSA has demonstrated a remarkable potential to spread in hospitals, with numerous outbreaks of infections described over the past 30 years. In addition, community acquired MRSA (CA MRSA) has been increasingly identified in community infections. Unlike hospital MRSA (HA MRSA), which are typically resistant to multiple antibiotics, the CA MRSA are susceptible to majority of the non β lactam antibiotic classes. Most transmission of HA MRSA from patient to patient is thought to be mediated by transiently colonised healthcare workers, although airborne dispersal and transmission through contacts with contaminated surfaces may also be important.

High prevalence of MRSA (35% in ward, 43% in ICU) in blood was observed by us in-vitro. There are reports of 30-85% MRSA prevalence from different parts of India. This high prevalence of MRSA as evident from previous years could be explained because of persistent high usage of cephalosporins and quinolones that predisposes to selection of MRSA. In India most of the HA MRSA belongs to type III and III A mec A cassetts. A small number of our S. aureus isolates (22) from OPD were analysed & most of these were positive for PVL gene but were mec A negative thereby indicating that such S. aureus were not CA-MRSA. However, our MRSA were subjected to MLST typing & were confirmed to belong to T329 clone that has Brazilian / Hungarian origin.

Glycopeptides remain the mainstay of the treatment of MRSA. No vancomycin resistant S. aureus (VRSA) has been reported from our institute, though there is a report of VRSA from India. Linezolid, tigecycline & daptomycin (0% resistance in all), are other alternatives to vancomycin in the event of adverse reactions or other reasons.

Similarly coagulase negative staphylococcus (CONS) obtained from ICU blood samples has shown high resistance to oxacillin (100%) and clindamycin (90%). Most of these isolates often considered as colonizers/contaminants were isolated as part of the surveillance of catheter related blood stream infections.

Vancomycin Resistant Enterococci (VRE)

Colonization and infection with VRE primarily affects moderately to severely ill patients in a tertiary care hospital. Most of the VRE reported from our hospital were from intensive care units (ICUs), oncology wards, or transplantation units and outpatient dialysis units. Exposure to broad spectrum antibiotic often was found to be a risk factor for infection or colonization with VRE; in particular, exposure to vancomycin/teicoplanin or cephalosporin. Other significant risk factors include the length of hospital stay, proximity to another patient colonized or infected with VRE as a result of the breach in hospital infection control.
control practices. Incidence of 10% VRE was documented at our hospital in vitro. Majority VRE were identified as E. fecium from our hospital. Similar VRE prevalence of 8, 5.5 and 23 per cent are noted in Delhi, Chandigarh and Mumbai, respectively. ß-lactam resistance in our hospital. Similar VRE prevalence of 8, 5.5 and 23 per cent are noted in Delhi, Chandigarh and Mumbai, respectively.

**Community Acquired Pneumonia**

Mostly community acquired pneumonia causing organism like Streptococcus pneumoniae, H. influenzae, Moraxella catarrhalis, S. aureus or K. pneumoniae from OPD samples have not been adequate. Organisms isolated in ten years have been Moraxella spp. (139), H. influenzae (53), ß-haemoytic streptococci (10) and E. coli (82). The number was inadequate for any meaningful evaluation. This could be due to high usage of empirical antibiotics by general practitioners, improper sample quality or quantity or inadequate isolation procedures. We observed 20% penicillin intermediate Streptococcus pneumoniae in ICU and overall prevalence for the same was 9.52% (2/20) (Fig 3), though higher level of resistance (26.7% intermediate resistance, 9.1% resistance) is seen in other parts of South East Asia.9

The nasopharyngeal carriage rate in children were documented as 6.5% by us10 and 15.4% of those were intermediate resistant. Recently UK has reported similar penicillin resistant pneumococci (PRP) (6.7%). Resistance to erythromycin (25%) and clindamycin (31%) have been detected in previous years. Resistance in H. influenzae and Moraxella were noted as 33%, 51%, 10%, 9%, 0%, 0% and 33%, 30%,0%,0%,0% to penicillin, quinolone, cotrimoxazole. cefuroxime, ceftriaxone and carbapenem, respectively.

**Enteric Fever**

Enteric fever is one of the commonest illness prevalent in the community capable of causing septicaemia with far reaching consequences even necessitating hospitalization11. On an average 34% of OPD blood culture positive samples (out of the total 19% OPD positives) yielded S. typhi followed by S. paratyphi A (15%). It was also noticed that infection with S. paratyphi A has almost doubled in the last 5 to 8 years at our center. Ampicillin, chloramphenicol and cotrimoxazole (ACC0) resistance documented in S.typhi was approximately between 38 to 40% in years 2001-2002 and ACC0 resistance was not seen in S. paratyphi A at the same time. The Nalidixic acid resistance in the year 2003 documented was 59.7%12. No resistance was documented by this time in S.typhi & paratyphi A to other antibiotics like fluoroquinones (Ciprofloxacin) and 3 generation cephapsporin (ceftriaxone). Soon after the year 2003 it was noticed that MICs in S.typhi for quinolones started increasing (>0.38 - 3 μg/ml). At this stage, nalidixic acid resistant S. typhi (NARST) isolates started increasing significantly (p < 0.001) and on an average 96% of isolates of S.typhi and paratyphi A were resistant to nalidixic acid by the year 2008. In the year 2006, 5.6% of S. typhi were found to develop high level ciprofloxacin resistance.13

However, by the end of the year 2008 high level ciprofloxacin resistance noticed was 21.6%. (Table 1) It was also noticed that sharp increase in nalidixic acid resistance in S. typhi was associated with appearance of high level resistance to fluoroquinolones. The appearance of NARST strain was associated with treatment failures on the floor when patients were treated only with quinolones. It appears that quinolones are no longer the drug of choice in enteric fever due to S.typhi.12 No resistance to cephalosporins has been documented up till now at our center in enteric fever due to S.typhi or paratyphi A.

**Multi drug Resistant Gram Negative Organisms**

1. **Extended spectrum beta-lactamase (ESBL)**

ESBL producing strains of enterobacteriaceae have emerged as a major problem in hospitalised as well as community based patients. In Indian hospitals ESBL- producing Klebsiella spp are predominant organisms responsible for high morbidity. ESBLs were first described in Germany in 1985. They are defined as enzymes with the ability to hydrolyse 3 generation cephalosporin and are inhibited by clavunate. The original ESBLs were point-mutation derivatives of the restricted-spectrum TEM and SHV enzymes commonly found in ampicillin resistant E. coli and Klebsiella spp.

In late 1990 there emerged a new resistance pattern of ESBL which were resistant to ceftriaxone but apparently susceptible to cefazedime. These organisms were found to carry new gene for ESBL known as CTX-M. Moreover there is a seismic shift as previously, the strains that produced TEM and SHV ESBLs were mostly Klebsiella spp. often in intensive care units14 but now a day's community E.coli are frequently carrying CTX-M ESBL. There is a spread of clonal Sequence Type (ST) 131, serotype O25 E. coli with CTX-M-15 in India and other parts of world15. The reason for the widespread dissemination of CTX-M enzymes was the recruitment of their genes by highly promiscuous plasmids, as with pCTX-M-3 in Poland, which has spread CTX-M-3 enzyme among many strains and species.

In a study at SGRH the ESBLs in nosocomial blood isolates were found to be 60.8% and 47.6% in E.coli and Klebsiella spp., respectively in the year 2008. In an Asian multi-centric SMART study, in which our centre also participated, for the community prevalence of ESBLs, high prevalence in E.coli (79%) and Klebsiella spp. (70%) was noted in the year 2006-2007.16 The treatment of choice for ESBL producing
organisms is carbapenems. Treatment with beta-lactam and beta-lactamase inhibitor combination drugs (BL-BLI), though sensitive in-vitro, may result in treatment failures due to inoculum effect or combination of ESBL/AmpC with porin loss. Finally, some CTX-M ESBLs may also be associated with carbapenem resistance in combination with porin loss or efflux.

2. AmpC

Shortly afterwards, AmpC β-lactamase emerged which were resistant to 3 generation cephalosporin including BL-BLI (in contrast to ESBL) but retained sensitivity to 4 generation cephalosporin (cefepeime/cefpirome). These are cephalosporinases that are found on the chromosomes of Enterobacter spp., Serratia spp., Citrobacter freundii, Proteus vulgaris, Providencia spp. and Morganella morganii. Transmissible plasmids have acquired genes for AmpC enzymes, which consequently can now appear in bacteria lacking or poorly expressing a chromosomal bla<sub>AmpC</sub> gene, such as E.coli, K. pneumonia, and P. mirabilis. Resistance due to plasmid-mediated AmpC may be both harder to detect and broader in spectrum.

In our laboratory a high incidence of AmpC has been noted in E. coli (72.4%) & K. pneumoniae (80.6%), which is much higher than reported (33.33% in Klebsiella pneumonia) from another hospital in Delhi<sup>17</sup>. The internationally accepted methodology for its identification are still evolving and are not yet standardized for the clinical laboratories. Variations were observed in the results by using cefoxitin discs obtained from different manufacturers.

Strains with AmpC genes are often resistant to multiple agents and the use of cephalosporins to treat infections with bacteria known to produce AmpC β-lactamase are prone to treatment failures regardless of the in-vitro susceptibility results. Carbapenems remains the treatment of choice for the AmpC producing organisms. If the isolate is susceptible, fluoroquinolone therapy appears to be an option especially for non-life threatening infections such as urinary tract infection. Tigecycline is another option except in urinary tract infections.

AmpC are also weak carbapenemases, its hyper-production in association with porin loss may even lead to carbapenem resistance and thus contributing in the emergence of pan-resistant organisms.

3. Carbenapenemase

Carbenapenems, such as imipenem and meropenem, are often used to treat infections caused by extended-spectrum beta-lactamase (ESBL) producing Gram-negative bacteria & other MDR afermenters. A new class of bacterial enzymes capable of inactivating carbapenems, known as K. pneumoniae carbapenemases (KPCs), has emerged. In 1996, the first isolate of KPC producing K. pneumonia was discovered in a clinical specimen from US<sup>18</sup> and since then has rapidly spread in the world. Carbapenemase can hydrolyze all penicillins, cephalosporins, and carbapenems. On one hand KPCs are playing havoc in Klebsiella and E.coli, and on the other hand another different class of carbapenemases, Metallo β-lactamase (MBLs) produced by Pseudomonas spp. and Acinetobacter spp. are having further devastating effect.

We have seen a high prevalence of carbapenemase resistance to imipenem/meropenem in E. coli, Klebsiella spp., Pseudomonas spp., Acinetobacter spp., in wards and ICU as 2&13%, 31&51%, 39 & 59% and 57 & 80%, respectively. Fig.4). However, lower carbapenem resistance in Klebsiella spp. (23.4%), Pseudomonas spp (28.2%) and Acinetobacter spp (48%) have been reported elsewhere<sup>20</sup>. Another report from Vellore, evaluating respiratory isolates also found lower resistance of 12.2% to carbapenems in afermenters<sup>20</sup>. Higher carbapenem resistance in our institute may be partly due to the increased scrutiny of ertapenem resistance strains for carbapenemase by Modified Hodge Test (MHT) and reconfirmation of imipenem/meropenem MIC be E-test, even though they were sensitive in-vitro by routine screening methods.

Another carbapenem, ertapenem introduced in 2008 is already showing high resistance of 61% in Klebsiella spp and 20% in E.coli. Ertapenem could be used, excepting in afermenters & may have Pseudomonas sparing effect unlike imipenem/meropenem which may increase multi-drug resistance in afermenters as a collateral damage. Tigecycline, introduced in 2007 in our hospital is another alternative drug for multi drug resistant organisms (except Pseudomonas spp.) but even resistance to this drug is rapidly increasing in Acinetobacter spp. (70%) & Klebsiella spp. (61%). (Fig.4)

The options for treating infections caused by KPCs are limited, and often require the use of colistin (polymyxins), which fell into disuse in the 1980s due to high rates of nephrotoxicity. Colistin resistance (8% in Pseudomonas spp) has also been documented from our institution (Fig.4). In ICU environments where carbapenemase/ESBL-producing microorganisms are increasingly isolated and colistin is the presumptive and/or microbiological treatment of choice, the emergence of colistin resistance poses a realistic threat compromising treatment choices and potentially the outcome of critically ill patients. Colistin should always be used in combination with other antimicrobials to have adequate activity and prevent resistance.

**Candida Spp.**

Rampant use of broad spectrum antibiotics has resulted in higher incidence of yeast infections. Frequently isolated yeast fungi in blood are non-candida albicans (84.8%) at our institution, especially in ICU. C. tropicalis (18.3%), C. albicans (13.2%), C. haemulonii (9.5%), C. glabrata 6.2% C. krusei 3.1% are the predominant isolates (Fig.1 & 2).

Most of the isolates were completely susceptible to amphotericin B and flucytosine, with exception of C. haemulonii that exhibits high level of resistance to these drugs. C. albicans...
remains sensitive to fluconazole and voriconazole. Resistance to amphotericin B (18.6%) and flucytosine (75.7%) is also observed in C. krusei. Similarly resistance to fluconazole is observed in C. tropicalis (10.9%), C. parapsilosis (55.5%) and C. glabrata (50%) in 2008. In the same year, resistance to voriconazole in C. glabrata (25%), C. tropicalis (3-4.4%), C. parapsilosis (6.5%) and C. haemulonii (22.6%) was noticed. Some isolates of pan resistant C. haemulonii (15 isolates) were tested against caspofungin, all were completely sensitive.

Prescription Auditing

Surveillance of antibiotic resistance when compared with antibiotic use in a health care facility during the same time period adds value to the findings. Usage of antibiotics as daily defined dose per 100 bed days is a good measure to know exact utilization of a particular antibiotic. Data generated using this standard methodology recommended by WHO is accepted for comparison with any other data such generated anywhere in the world. Study of prescription auditing is a valuable tool to know the prescribing habits of health care providers at a particular hospital. It also indicates possibility of peer pressure or promotion of any particular antibiotic molecule in a particular health care setting. Time series analysis of antibiotics usage and development of resistance are reliable investigations that provide in depth understanding of antibiotic usage and development of resistance at a given demographic settings. However, discussion regarding antibiotic use is beyond the scope of this article.

Conclusion

Surveillance of antibiotic resistance in hospital flora & pathogens is an investment for future use. The data thus generated can provide an in depth knowledge regarding impending treatment failures and gives a chance to the physician for appropriate therapy that can be initiated right in the beginning, thereby decreases mortality. Multi drug resistant organisms like MRSA, VRE, PRP, ESBL, AmpC and Carbapenemase producing organisms have come to stay and need to be treated with care and prudence. The above statement become more serious when we know that there are no research molecules in pipeline.

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References