Changing Trends in Antimicrobial Susceptibility and Hospital Acquired Infections Over an 8 Year Period in a Tertiary Care Hospital in Relation to Introduction of an Infection Control Programme

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Abstract

Introduction: Antimicrobial resistance patterns in Indian hospitals differ from that reported in Western hospitals in having a high prevalence of resistance among Gram negative bacteria and a much lower incidence of resistant Gram positive bacteria. The long term effect of infection control programs on this situation also is unclear. We attempt to describe changes in our hospital antibiogram, incidence of infections due to MDR-O and VAP/CrBSI over an 8 year period in relation to introduction and serial modifications of an infection control program.

Methods: A retrospective review of surveillance and hospital antibiogram data over the period 2001-2008 with an accent on selected MDR-O, was undertaken. All infection control protocols and modifications were also documented over the same period.

Results: We found a 65% ESBL production rate in E.coli and Klebsiella and up to 40% and 70% of Pseudomonas and Acinetobacter respectively were resistant to carbapenems. While MRSA constituted 40-50% of all Staph aureus isolates, VRE and C.difficile were rarely encountered. Carbapenem resistance in Klebsiella has begun to emerge from 2005. CrBSI were largely Gram negative with MRSA contributing 6% of all isolates only. Over the 8 year study period, infection control efforts resulted in reduced CrBSI/VAP rates, fewer MRSA infections and improved sensitivities for Pseudomonas but not for other organisms.

Conclusions: Resistance among Gram negative pathogens (especially ESBL production in Enterobacteriaceae and carbapenem resistance in Pseudomonas and Acinetobacter) is a major problem in our tertiary care hospital. On the other hand C.difficile and VRE are rarely encountered. Infection control measures were modestly effective in reducing CrBSI/VAP rates but resistance rates among Gram negative pathogens were not significantly lowered.

Introduction

Antimicrobial resistance is an increasing problem worldwide as well as in Indian hospitals. An increasing prevalence of MDR-O (multi-drug resistant organisms) such as MRSA (methicillin resistant Staphylococcus aureus), ESBL (extended spectrum beta-lactamase) producing enterobacteriaceae and carbapenem resistant Pesudomonas and Acinetobacter has been reported from various Indian centres. On the other hand, though Clostridium difficile and VRE (vancomycin resistant enterococcus) have emerged as prominent nosocomial pathogens in the west, they are apparently much less common in Indian hospitals. We studied the prevalence and epidemiology of MDR-O and nosocomial infections at our institution between 2001 and 2008. We also document the institution and evolution of an infection control programme and attempt to correlate this with changes in nosocomial infection rates and serial antibiograms over time.

Materials and Methods

Apollo Speciality Hospital (ASH) is a 230 bedded tertiary care cancer hospital with large bone marrow transplant and neurosurgical and orthopedic units. We retrospectively analysed hospital surveillance records between the periods January 2001 and December 2008. We monitored the following indices:

1. The number of positive isolates for each MDR-O (as a percentage of all specimens received by the microbiology lab for that period) was determined every 3 months and analyzed longitudinally over the eight year period of the study (Fig. 1). The isolates were predominantly from hospitalized patients as outpatients constitute a minority of cultures received by the microbiology laboratory. We also analysed incidence rates of VRE (Fig. 1a) and C. difficile toxin positivity (Fig. 1b).

2. Antibiogram: Sensitivity patterns as determined by Kirby – Bauer disc diffusion testing for all isolates from hospitalized patients was used to devise the hospital antibiogram as per CLIA guidelines. This was updated and analysed every 3 months for the entire period of the study. We specifically looked at the rates of

a. MRSA prevalence (as a percentage of all Staph aureus isolates – Fig. 2)

b. Prevalence of ESBL producing E.coli (as a percentage of all E.coli isolates- Fig. 3) and Klebsiella (as a percentage of all Klebsiella isolates- Fig. 4). We determined presumptive ESBL producing status based on resistance to ceftazidime.

c. Carbapenem resistant Pseudomonas aeruginosa (Fig. 5)

3. We analysed the hospital wide incidence of CRBSI (catheter related blood stream infections) and VAP (ventilator associated pneumonia) monthly from October 2003 to 2008, as defined by standard surveillance criteria.

4. We documented serial introduction and modifications in the hospital infection control program as per minutes of infection control committee meetings (Table 1).
Figure 1b shows that despite frequently ordering C. difficile toxin assays in patients with antibiotic associated diarrhea, only 1-5 positive cases were seen annually, with complete absence in some years. Only 2.67% of all toxin assay tests over an 8 year period turned out to be positive. Toxin A detection kits by the ELISA method were used till 2006, after which toxin A and B detection kits were used. This low incidence was despite a high index of suspicion for C. difficile in patients with antibiotic associated diarrhea and extensive testing. Even after the outbreak of C. difficile reported in western hospitals from 2005 onwards, our hospital continued to show low rates.

Figure 2 shows the prevalence of MrSA as a percentage of all Staph aureus isolates. MrSA prevalence rates ranged from 12-73% with an overall slight increase from 40% to 50% over the study period. However the number of new MrSA isolates started dropping in 2008, possibly in relation to enhanced hospital wide MRSA screening and contact isolation initiated in 2007 (fig 1).

Figure 3 shows changes in E. coli sensitivities over time. Sensitivity to ciprofloxacin remained consistently low at 15% throughout the study period (fig 3a). Sensitivity to ceftazidime (a surrogate marker for ESBL production) gradually declined from 37% in 2001 to 27% in 2008 with an average of about 35% (fig 3b), reflecting a rising ESBL production rate from 63% to 73% and an average ESBL prevalence of 65%. Sensitivity to

Results

Figure 1 shows that the most prevalent MDR-O at our hospital were ESBL producing E.coli and Klebsiella, several times higher than other pathogens. This remained true throughout the 8 year study period. MDR-Pseudomonas and MRSA were encountered, but at much lower frequencies compared to ESBL producers.

Figure 1a shows that despite a high volume of cultures received by the lab, VRE was encountered only 1-3 times a year, and never in some years.

Figure 1b shows that despite frequently ordering C. difficile toxin assays in patients with antibiotic associated diarrhea, only 1-5 positive cases were seen annually, with complete absence in some years. Only 2.67% of all toxin assay tests over an 8 year period turned out to be positive. Toxin A detection kits by the ELISA method were used till 2006, after which toxin A and B detection kits were used. This low incidence was despite a high index of suspicion for C. difficile in patients with antibiotic associated diarrhea and extensive testing. Even after the outbreak of C. difficile reported in western hospitals from 2005 onwards, our hospital continued to show low rates.

Figure 2 shows the prevalence of MRSA as a percentage of all Staph aureus isolates. MRSA prevalence rates ranged from 12-73% with an overall slight increase from 40% to 50% over the study period. However the number of new MRSA isolates started dropping in 2008, possibly in relation to enhanced hospital wide MRSA screening and contact isolation initiated in 2007 (fig 1).

Figure 3 shows changes in E. coli sensitivities over time. Sensitivity to ciprofloxacin remained consistently low at 15% throughout the study period (fig 3a). Sensitivity to ceftazidime (a surrogate marker for ESBL production) gradually declined from 37% in 2001 to 27% in 2008 with an average of about 35% (fig 3b), reflecting a rising ESBL production rate from 63% to 73% and an average ESBL prevalence of 65%. Sensitivity to
imipenem was consistently close to 100% (fig 3c) through out the study period except for a 6 month period in 2001 between May to December (possibly due to errors in disc methodology). Sensitivity to cefoperazone-sulbactam (fig 3d), piperacillin-tazobactam (Fig 3e) was as shown. In our institution the sensitivities to cefoperazone-sulbactam were marginally better at close to 80% versus piperacillin-tazobactam at around 70%.

Figure 4 shows changes in Klebsiella sensitivities over time. Sensitivity to ciprofloxacin remained consistently low at 35-40% through out the study period (Fig. 4a). Sensitivity to ceftazidime (a surrogate marker for ESBL production) remained around 35% throughout the study period (Fig. 4b), indicating a 65% rate of ESBL production among Klebsiella isolates. Sensitivity to imipenem was close to 100% till 2005, but then started declining (Fig. 4c). Sensitivity to cefoperazone-sulbactam (Fig. 4d) and piperacillin-tazobactam (Fig. 4e) was as shown with cefoperazone-sulbactam again being slightly more effective versus 70% of isolates versus piperacillin-tazobactam at around 60%.

Figure 5 shows changes in Pseudomonas sensitivities over time. Sensitivity to ciprofloxacin remained consistently low at 40-50% through out the study period (Fig 5a). Sensitivity to ceftazidime rose from 45% to 60% over the study period (fig 5b). Sensitivity to imipenem rose from around 50% to around 70% over the study period (Fig. 5c). Sensitivity to cefoperazone-sulbactam rose in similar fashion (Fig. 5d). These were the only improvements in Gram negative sensitivity profile we could note in our study. Sensitivity to piperacillin-tazobactam (Fig.
We tracked Acinetobacter sensitivities between 2006 and 2008 only after noting an increased incidence of the organism in later years. Figure 6 shows carbapenem sensitivity in Acinetobacter isolates remained around 30% over this time period.

We started tracking CRBSI and VAP rates after 2003. Figure 7a and 7b show monthly and yearly changes respectively in CRBSI rates between 2003 and 2008, showing a decrease from 20 to 12 per 1000 line days, which however remains 3-4 times that reported in the western literature.9

Figure 8 shows the causative agents of CRBSI over the period.
### Table 1: Chronology of Infection Control at ASH

<table>
<thead>
<tr>
<th>Year</th>
<th>Policy</th>
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| April 2001 | - establishment of IC program and IC committee  
- surveillance and hospital antibiogram initiated  
- one infection control advisor (ID physician) and 3 part time IC nurses appointed  
- policy on contact isolation of MDRO (MRSA, ESBL, carbapenem resistant Pseudomonas) including one on one nursing  
- respiratory isolation for TB started  
- 500ml alcohol dispensers for hand hygiene approved for installation in all rooms and in other nursing areas  
- surveillance for central line infections and VAP initiated  
- needlestick registry and PEP initiated |
| July 2001  | - lecture on infection control to all hospital consultants  
- puncture proof container for sharps at each bedside provided  
- towels replaced with disposable tissue paper for drying after handwashing  
- infection control manual for hospital written and adopted |
| August 2001| - meeting with all surgeons on antibiotic prophylaxis guideline formulation  
- antibiotic protocol for surgical prophylaxis introduced with emphasis on starting antibiotic within one hour of skin incision  
- antibiotics specified for each type of surgery  
- duration of post-op antibiotics reduced from 7 to 2-4 days with aim of long term movement towards a single dose |
| October 2001| - provisional adoption of a surgical prophylaxis policy  
- infection control week for health care workers organized  
- free administration of 3 doses of HBV vaccine for all nurses started  
- standardized protocol for ventilator management introduced  
- disposable gowns introduced for contact isolation  
- typhoid vaccine introduced for all food handlers  
- color coded bins for waste segregation introduced |
| January 2002| - glutaraldehyde storage of forceps on dressing trays eliminated, forceps to be sterilized and packed  
- formalin tablet fumigation eliminated |
| March 2002 | - mandatory wearing of gloves for phlebotomists  
- finalization of surgical prophylaxis policy  
- antibiotic prophylaxis duration reduced to 48 hrs |
| April 2002 | - one full time IC nurse appointed  
- elimination of flimsy plastic gloves, replacement by latex gloves |
| June 2002  | - lab to stop reporting ceftazidime sensitivities, consultants advised not to prescribe drug  
- single room isolation for all MRSA patients approved  
- administration of pre-op antibiotic started in OT, not in ward |
| July 2002  | - IC committee to be notified whenever building works are carried out  
- same day or previous day admission for elective surgery advised  
- Staph aureus screening by nasal swabs pre-op initiated for elective surgery  
- previous day pre-op shaving eliminated for surgery, clipping introduced |
| November 2002| - central line protocol introduced (sterile placement, removal of femoral lines by day 5, use of antiseptic impregnated catheters for high risk cases) |
| January 2003| - standard precautions and routine protocols for HIV infected patients undergoing surgery introduced  
- post-exposure prophylaxis emphasized  
- educational program for HIV introduced |
| June 2003  | - nasal swab screening for Staph aureus eliminated for elective surgery  
- surveillance for CRBSI and VAP commenced |
| November 2003| - closed bag system for IV fluids introduced on selected basis  
- removal of femoral lines by day 5 recommended  
- single use vials recommended for all medications  
- puncture proof bedside sharps container introduced, cutting and burning of needletips eliminated |
| December 2003| appropriate barrier precautions introduced whenever building works carried out to prevent Aspergillus outbreaks |
| March 2004 | - N-95 masks for respiratory isolation introduced  
- 10% povidone iodine to replace lower strengths  
- antibiotic prophylaxis for surgery reduced to 24hrs |
| May 2004   | switch to collapsible bags for IV fluids hospital wide, elimination of vented plastic bottles |
| July 2004-August 2004 | use of 2% chlorhexidine for skin preparation prior to bedside procedures introduced  
- varicella vaccination for nurses treating high risk neutropenic patients introduced  
- infection control junior officer appointed to assist infection control advisor  
- nasal swab screening selectively for MRSA introduced for ICU, with follow up contact isolation and decolonization with mupirocin |
| October 2004| 100ml handrub dispenser mounted on each bedrail instead of 500ml in each room |
| January 2005| policy for neutropenic patients introduced (ultra-violet light for room disinfection before use after construction, sign outside door, N-95 masks for patients when transported, elimination of surgical masks for staff) |

*Contd.*
of the study. Gram positive cocci constituted 27% of isolates, Gram negative bacilli 56% and Candida 17%. The proportion of Gram negative CRBSI was much higher than that reported in western hospitals. MRSA constituted 6% of all episodes.

Figure 9 shows a slight decline in VAP over time from 22 to 10 per 1000 ventilator days.

Table 1 shows the introduction and serial changes in infection control policies over time. Notable policies were restriction of ceftazidime in 2002, initiation of an antimicrobial stewardship in 2006 and hospital wide MRSA screening followed by contact isolation and decolonization for all new admissions in 2007. Some observed favorable outcomes were:

- Reduced MRSA incidence (though the prevalence as a percentage of all Staph aureus actually rose) after screening was noted (fig 1 and 2).
- Improvement in ceftazidime sensitivity for Pseudomonas from 45% to 60% after discouraging use of this antibiotic was noted. Pseudomonas also showed improved sensitivities to carbapenems and cefoperazone-sulbactam over time.
- CRBSI and VAP rates both fell over the 5 year period of surveillance, possibly due to implementation protocols/bundles of care.

**Discussion**

We were successful in completing a longitudinal single center study of antimicrobial resistance and rates of hospital acquired infection, over a period of 8 years. Our study shows that ESBL producers were the most important MDR-O encountered in our hospital, being much more common than any other MDR-O. ESBL production among E.coli and Klebsiella was ~65% throughout the study period. This pattern has been well documented in Indian hospitals (2,3,4) but is only now emerging in hospitals in the western world.10 Ciprofloxacin sensitivity was very low at 15% and 35-40% for E.coli and Klebsiella respectively, essentially ruling out quinolones as empiric antimicrobial therapy for hospital acquired infections.

Carbapenems are considered the drugs of choice for ESBL producers and our study showed 100% sensitivity in E.coli isolates. However our data disturbingly documents emerging carbapenem resistance in Klebsiella species from 2005 onwards, similar to recent trends noted in western hospitals.

The beta-lactam/betalactamase inhibitors (cefoxoperazone-sulbactam and to a lesser extent piperacillin-tazobactam) remained useful drugs against Pseudomonas and low inoculum ESBL infections, as shown by others.2,12 These agents retained value as workhorse drugs for nosocomial infections especially in less severely ill patients with low inoculums infections, and play a valuable role as “carbapenem sparsers” in antimicrobial stewardship programs.

Carbapenem resistant Pseudomonas was the second serious Gram negative MDR-O though sensitivity rose from 50-70% through our study period, perhaps due to introduction of antimicrobial stewardship. Ciprifloxacin sensitivities of 40-50% again precluded quinolone use as empiric therapy. However ceftazidime and cefoperazone-sulbactam sensitivities actually improved over our study period, possibly due to restriction of ceftazidime.

Carbapenem resistance in Acinetobacter was widespread, with only 30% of isolates being sensitive. Carbapenems therefore can no longer be relied on as empiric therapy for these organisms, leading to an increase in use of alternatives such as colistin. We are currently monitoring colistin resistance at our center.

MRSA prevalence rates were 40-50% at our institution, on par with American centers. MRSA therefore remains a significant pathogen warranting empiric coverage in the appropriate clinical situation.

Both VRE and C. difficile remained rare with only a handful of cases throughout the 8 year study period, a remarkable contrast to the situation seen in the west. Continued vigilance with surveillance for these pathogens and immediate contact isolation are important to maintain this favorable situation.

The majority of our isolates (56%) from patients with CRBSI were Gram negative. Staph aureus (including 6% MRSA) constituted only 17% of all CRBSI. These data support guidelines calling for both Gram positive and Gram negative coverage for patients with suspected CRBSI, pending culture results.

We introduced a comprehensive hospital infection control program in 2001, with emphasis on hand hygiene and contact isolation. We periodically added other measures such as MRSA screening and antimicrobial stewardship. CRBSI/VAP rates both declined over the 5 years of monitoring possibly due to implementation of protocols/bundles of care. The incidence of new MRSA infections also decreased after February 2007. It is possible that hospital wide institution of a screening

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**Table 1: Chronology of Infection Control at ASH - (Contd..)**

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<th>Year</th>
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<tbody>
<tr>
<td>May 2005</td>
<td>-ESBL accepted as a hospital wide problem, isolation discontinued for ward patients</td>
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<tr>
<td></td>
<td>-early Foley catheter removal emphasized</td>
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<tr>
<td>October 2005</td>
<td>ESBL isolation discontinued hospital wide</td>
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<tr>
<td>February 2006</td>
<td>-notifiable diseases list drawn up and submitted to Govt periodically</td>
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<tr>
<td>March 2006</td>
<td>-antimicrobial stewardship initiated by restricting carbapenems and linezolid with pharmacy tracking of use of these antibiotics, and IC officer feeding back to consultants after 48 hrs of use</td>
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<tr>
<td>March 2007</td>
<td>-adherence to hand hygiene monitored in ICU</td>
</tr>
<tr>
<td>July 2006</td>
<td>MRSA screening extended to Neurology ICU and high risk neutropenic patients</td>
</tr>
<tr>
<td>November 2006</td>
<td>intensive cleaning of ICU surfaces commenced</td>
</tr>
<tr>
<td>February 2007</td>
<td>MRSA screening extended hospital wide</td>
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<tr>
<td>March 2007</td>
<td>-circular issued mandating ID consultation when restricted antibiotics used beyond 48hrs</td>
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<tr>
<td>August 2007</td>
<td>-teicoplanin and vancomycin removed, polymyxins added to restricted antibiotics</td>
</tr>
<tr>
<td>January 2008</td>
<td>chlorhexidine bathing for all patients in ICU and oral decontamination for ventilated patients introduced</td>
</tr>
<tr>
<td>August 2008</td>
<td>-elimination of white coats and recommendation against long sleeves, ties and wrist watches</td>
</tr>
<tr>
<td></td>
<td>-teicoplanin and vancomycin removed, polymyxins added to restricted antibiotics</td>
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program with subsequent contact isolation and decolonization contributed to this decline. We did note improvement in ceftazidime, imipenem and cefoperazone-sulbactam sensitivities among Pseudomonas isolates, possibly related to antibiotic restriction or stewardship.

Results in terms of improvement in antimicrobial sensitivity profiles (except for Pseudomonas) were disappointing. However in the absence of a placebo group, it is possible that rates may have been even higher without our interventions. It appears that our MDR-O antibiotics were largely uninfluenced by infection control efforts, including institution of an antimicrobial stewardship program. Probable reasons include inadequate adherence to protocols existing on paper or absence of effective policing of clinicians when antimicrobials were inappropriately used. Besides, widespread ESBL prevalence rates in the community at large and importation of cases from other hospitals to our referral center may have negated efforts within our center.

The strength of our study was the 8 year follow up period which allowed us to draw conclusions about the emergence of resistance over a prolonged period of time. We acknowledge the limitations of disc diffusion antimicrobial susceptibility testing and use of ceftazidime resistance as a surrogate marker of ESBL production. However this practice is similar to the situation in most hospital microbiology laboratories in India and we believe our findings reflect the ground realities of resistance existing elsewhere in India.

In conclusion, or study shows that Gram negative pathogens such as ESBL producing Enterobacteriaceae and carbapenem resistant Pseudomonas and Acinetobacter are common in Indian hospitals. Such a scenario appears likely to persist in the near future, with important implications for antimicrobial selection and infection control policies. For instance, empirical coverage for any nosocomial infection should include ESBL coverage, drastically restricting the number of antibiotic choices available. Carbapenem resistance in Klebsiella has also worryingly begun to emerge from 2005.

Among Gram positive pathogens, MRSA is a significant pathogen while VRE and C.difficile remain very uncommon, in sharp contrast to the situation in western hospitals. CRBSI are usually caused by Gram negative bacteria with MRSA contributing a small proportion only. Infection control measures including hand hygiene, antimicrobial stewardship, VAP/CRBSI bundles, MRSA screening and ceftazidime restriction appeared to be modestly effective in our study. Such infection control programs clearly need to be scaled up and implemented more effectively to contain this bleak resistance scenario.

References