Antibiotic Stewardship- Preserving Today's Antibiotic Armamentarium

Emerging PDR Gram-negative bacteria in South Africa

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Scope of the presentation

• Why do we all need antibiotic stewardship as a matter of urgency
  • Global spread of extended spectrum beta-lactamases (ESBLs)
  • Global spread of carbapenem resistant *Enterobacteriaceae* (CRE)

• Local spread of CRE

• What is antibiotic stewardship

• Practically, how to commence with a antibiotic stewardship programme (ASP)
  • Step 1: Develop an interdisciplinary team and define the roles and responsibilities of team members
  • Step 2: Do a survey of current practices
  • Step 3: Select strategies by which to execute an ASP
  • Step 4: Present results of ASP projects to the clinicians/medical staff

• Conclusions
Why do we all need antibiotic stewardship as a matter of urgency?
Noteworthy β-lactamases produced by Gram-negative bacilli (GNB) such as *E.coli* and *K.pneumoniae*, causing significant infections worldwide include:

- Extended-spectrum β-lactamases (ESBLs)
- Carbapenemases

ESBLs hydrolize most beta-lactams and cause resistance except to the carbapenems:

- 1<sup>st</sup> generation cephalosporins e.g cefazolin
- 2<sup>nd</sup> generation cephalosporins e.g cefuroxime
- 3<sup>rd</sup> generation cephalosporins e.g ceftriaxone, ceftazidime, cefotaxime
- 4<sup>th</sup> generation cephalosporins e.g cefepime

Beta-lactam β-lactamase inhibitors e.g ampicillin-sulbactam, amoxycillin clavulanate and piperacillin-tazobactam

And are usually resistant to quinolones and aminoglycosides via additional genes carried with the ESBL gene
ESBL –producing pathogens in intra-abdominal infections

SMART (Study for the Monitoring of Antimicrobial Resistance Trends) 2004-2009

Resistance to following:
- ceftriaxone 29.7%
- cefotaxime 28.7%
- ciprofloxacin 22.5%
- levofloxacin 21.1%

South Africa
(n=1218 GNB)

E.coli 7.6% ESBL+
K.pneumoniae 41.2% ESBL+

MDR Rate: ≥ 3 classes:
K. pneumoniae 27.9%
Enterobacter spp 14.9%
E.coli 4.9%

Comparative international ESBL rate in complicated Intra-Abdominal Infections:

Carbapenem resistance amongst *Enterobacteriaceae* can be conferred by several genetic mechanisms but epidemiologically, the most important of these result in the production of β-lactamases (carbapenemases) which hydrolyse carbapenems and most other beta-lactams.

The carbapenemases belong to different classes and include:

- *Klebsiella pneumoniae* carbapenemases (KPC)
- Metallo-beta-lactamases (MBL), such as
  - Verona integron-encoded MBLs (VIM)
  - New Delhi Metallo-β-lactamases (NDM-1)
- OXA-48-like carbapenemases such as OXA-48, OXA-181 etc.
Global spread of KPC-producing bacteria

- Brink et al. *J Clin Micro* 2012;50:525-527
Global spread of NDM-producing bacteria

Nordmann et al. *Emerg Infect Dis* 2011;17: 1791-1798 (Reproduced with permission)
Brink et al. *J Clin Micro* 2012;50:525-527
Spread of OXA-48-like producing bacteria in the EU, ME and Africa

Nordmann et al. Emerg Infect Dis 2011;17: 1791-1798 (Reproduced with permission)
Emergence (+/- outbreaks +/- inter-hospital spread) of colistin-resistant KPC

Mammina et al. *Euro Surveill* 2012;17:1-6
...and recently emergence of colistin-resistant NDM in *K. pneumoniae*
and recently emergence of colistin-resistant OXA-181 in *K. pneumoniae*
Local emergence and spread of carbapenem-resistant Enterobacteriaceae (CRE)
Emergence of extensive drug resistance (XDR) among Gram-negative bacilli in South Africa looms nearer

Adrian Brink, Charles Feldman, Guy Richards, Johan Moolman, Martthinus Senekal

Until recently, the term ‘extensive drug resistance’ (XDR) was held to be applicable to *Mycobacterium tuberculosis* only. It is now clear that Gram-negative bacilli are moving a step closer towards acquiring similar resistance. The emergence of multi-drug resistant (MDR) and pan-drug resistant (PDR) Gram-negative health care-associated pathogens has been confined to non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. However, increasing reports of infections due to XDR fermentative Enterobacteriaceae such as *Klebsiella pneumoniae*, *Escherichia coli*, Enterobacter spp. and even *Salmonella* spp. support the notion that ‘… MDR, XDR and PDR Gram-negative fermenters might become our worst nightmare’.15
Table I. Antibiotic resistance (%) among bacteraemic strains of selected Gram-negative pathogens in private institutions in 7 major centres* in South Africa, July December 2007

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>E. coli (N=503) Overall (range)</th>
<th>K. pneumoniae (N=548) Overall (range)</th>
<th>Enterobacter spp. (N=190) Overall (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>82 (65 - 90)</td>
<td>100 (-)</td>
<td>100 (-)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>39 (0 - 57)</td>
<td>62 (31 - 73)</td>
<td>99 (91 - 100)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>18 (0 - 33)</td>
<td>62 (31 - 72)</td>
<td>83 (0 - 96)</td>
</tr>
<tr>
<td>Ceftriaxone/cefotaxime</td>
<td>7 (0 - 15)</td>
<td>57 (43 - 66)</td>
<td>62 (44 - 91)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>5 (0 - 14 )</td>
<td>54 (50 - 64)</td>
<td>26 (10 - 46)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>9 (0 - 23)</td>
<td>49 (26 - 67)</td>
<td>38 (17 - 66)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>16 (0 - 36)</td>
<td>39 (18 - 64)</td>
<td>16 (0 - 40)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>16 (0 - 36)</td>
<td>39 (28 - 64)</td>
<td>16 (0 - 40)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>14 (0 - 32)</td>
<td>31 (0 - 43)</td>
<td>25 (10 - 52)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>6 (0 - 15)</td>
<td>25 (8 - 50)</td>
<td>6 (0 - 16)</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2 (0 - 8)</td>
<td>2 (0 - 8)</td>
<td>5 (0 - 17)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1 (0 - 6)</td>
<td>1 (0 - 1)</td>
<td>1 (0 - 5)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 (0 - 6)</td>
<td>1 (0 - 1)</td>
<td>1 (0 - 5)</td>
</tr>
<tr>
<td>% ESBL production</td>
<td>5 (0 - 11)</td>
<td>50 (33 - 59)</td>
<td>23 (9 - 37)</td>
</tr>
</tbody>
</table>

*Johannesburg, Pretoria, Durban, Cape Town, Bloemfontein, Port Elizabeth and East London.
ESBL = extended-spectrum B-lactamase.
Emergence of New Delhi Metallo-Beta-Lactamase (NDM-1) and Klebsiella pneumoniae Carbapenemase (KPC-2) in South Africa

Adrian J. Brink,a Jennifer Coetzee,b Cornelis G. Clay,b Sindi Sithole,c Guy A. Richards,d Laurent Poirel,e and Patrice Nordmann,e

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This report documents emergence of New Delhi metallo-beta-lactamase (NDM-1) and Klebsiella pneumoniae carbapenemase (KPC-2) in K. pneumoniae and Enterobacter cloacae in South Africa. NDM-1 producers have not been described in South Africa, and this is the first instance that KPC producers have been identified in Africa. The two patients infected with these carbapenemase-producing bacteria demised.
**ALERT:** Clinical microbiology considerations related to the

All carbapenem non-susceptible *Enterobacteriaceae* identified by automated susceptibility testing (Vitek 2) to be referred for molecular screening

Healthcare providers are informed that these organisms are a serious public health issue and pose a major threat to the viability of currently available antibiotics.
New, effective antibiotics are only likely to become available in 15 - 20 years. To prevent deaths from untreatable Gram-negative infections in South Africa, the rights of any doctor, whether in general or in hospital practice, to indiscriminately prescribe whatever antibiotic they wish, and in whatever fashion, must be challenged. Furthermore, although prevention of the emergence and subsequent spread of carbapenem-resistant Enterobacteriaceae (CRE) has focused on acute and chronic care facilities and *inter alia* on antibiotic exposure in these institutions, CRE may soon become an issue within entire communities, highlighting a role for public health authorities in CRE prevention efforts.

EDITORIAL

Wake up, South Africa! The antibiotic ‘horse’ has bolted

July 2012, Vol. 102, No. 7  SAMJ

Marc Mendelson  
President, Infectious Diseases Society of Southern Africa  
President, Federation of Infectious Diseases Societies of Southern Africa

Andrew Whitelaw  
Chairperson, Infection Control Society of Southern Africa

Mark Nicol  
Chairperson, South African Society for Clinical Microbiology

Adrian Brink  
Co-Chair, South African Antibiotic Stewardship Programme
Emergence and spread of carbapenem-resistant *Enterobacteriaceae* in South Africa

Brink et al. *J Clin Micro* 2012;50:525-527
Molecular screening of carbapenem non-susceptible Enterobacteriaceae in South Africa

Department of Clinical Microbiology and Molecular Biology, Ampath National Laboratory Services, National Reference Laboratory, Centurion

- N=403 carbapenem non-susceptible Enterobacteriaceae (mostly ertapenem NS) (1\textsuperscript{st} Feb 2011-31\textsuperscript{st} Oct 2012)
  
  Multiplex PCR according to Monteiro et al.

- 19% of Enterobacteriaceae tested contained a CRE gene (77/403)
  
  - OXA-48-like (n=40)
    - OXA-181 (n=30)
    - OXA-48 (n=10)
  
  - VIM (n=16)
  
  - GES (n=8)
  
  - KPC (n=4)
  
  - NDM (n=9)(excludes the 1\textsuperscript{st} report and outbreak, n=10)
  
  - IMP (n=0)


Brink et al. *SAMJ* 2012:102:599-601

What is antibiotic stewardship
What is antibiotic stewardship

- Stewardship is an ethic that embodies responsible planning and management of resources.

- The concept of stewardship has been applied in diverse realms, including with respect to environment, economics, health, property, information, and religion, and is linked to the concept of sustainability.

- Historically, stewardship was the responsibility given to household servants to bring food and drinks to a castle dining hall.

- The term continues to be used in many specific ways, but it is also used in a more general way to refer to a responsibility to take care of something belonging to someone else.

- To be a steward, and or act in steward to something, is known as stewardship.
Aims of antibiotic stewardship

- Optimise patient outcomes
- Minimise increases in antibiotic resistant organisms within our hospitals
- Maintain effectiveness of currently available antibiotics
- Ultimately reduce costs
- Build collaborative relationships and improve communication, trust and sharing of knowledge with other members of the healthcare team but most importantly with the clinicians

Mendelson et al. 1st South African Antibiotic Stewardship Program workshop, Sandton, Johannesburg, February 2012
Strategies for Antimicrobial Stewardship

Prospective audit of antimicrobial use with intervention and feedback

- Antimicrobial order forms
- Parenteral to oral conversion
- Dose optimisation
- Streamlining or de-escalation
- Combination therapy
- Formulary restriction and pre-authorisation
- Education
- Guidelines and clinical pathways
- Antimicrobial cycling

Dellit TH. Clin Infect Dis. 2007;44:159-177
“Education is considered to be an essential element of any program designed to influence prescribing behavior and can provide a foundation of knowledge that will enhance and increase the acceptance of stewardship strategies.”

“However, education alone, without incorporation of active intervention, is only marginally effective in changing antimicrobial prescribing practices and has not demonstrated a sustained impact.”

IDSA = Infectious Diseases Society of America
SHEA = Society for Healthcare Epidemiology of America

Dellit TH et al. Clin Infect Dis 2007;44:159-177
Practically, how to commence with a antibiotic stewardship programme (ASP)
What works: Tools to get started

Practically,

Step 1: Develop an interdisciplinary team and define the roles and responsibilities of team members

Step 2: Do a survey of current practices

Step 3: Select strategies by which to execute an ASP

Step 4: Present results of ASP projects to the clinicians/medical staff
Step 1
Develop an interdisciplinary team
Antimicrobial Stewardship Team

A team of individuals?

Or one synchronized team?
Step 2
Survey of current practices
Antibiotic prescription practices and their relationship to outcome in South African intensive care units

- Prevalence of Infection in South African Intensive Care Units (PISA) Study

- The study population comprised public and private sector hospitals in South Africa that were included in part I of the National Critical Care Audit.

- To ensure a true South African representation, adult and paediatric ICUs in the private and public (tertiary, regional and community level) sectors were included.

- n= 248 patients

Antibiotic prescription practices and their relationship to outcome in South African intensive care units

<table>
<thead>
<tr>
<th></th>
<th>Public</th>
<th>Private</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>85(34.3)</td>
<td>163(65.7)</td>
<td>248</td>
</tr>
<tr>
<td><strong>Antibiotics prescribed</strong></td>
<td>62(72.9)</td>
<td>120(73.6)</td>
<td>182(73.4)</td>
</tr>
<tr>
<td><strong>Inappropriate Empiric Antibiotic</strong></td>
<td>27(43.5)</td>
<td>73(60.8)</td>
<td>100(54.9)</td>
</tr>
<tr>
<td><strong>De escalation practiced</strong></td>
<td>9(33.3)</td>
<td>12(19.7)</td>
<td>21(23.9)</td>
</tr>
<tr>
<td></td>
<td>n=27</td>
<td>n=61</td>
<td>n=88</td>
</tr>
<tr>
<td><strong>Inappropriate duration of antibiotics</strong></td>
<td>33(55.9)</td>
<td>98(79.7)</td>
<td>131(72)</td>
</tr>
</tbody>
</table>

Antibiotic prescription practices and their relationship to outcome in South African intensive care units

Fig. 1. Simultaneous prescription of antibiotics.

Step 3
Select strategies by which to execute an ASP

ASP strategies to prevent carbapenem-resistant *Enterobacteriaceae* (CRE)
Risk factors for CRE acquisition or infection in South Africa:

1st. Inappropriate exposure to antibiotics
Consequences of inappropriate Rx: Collateral Damage

- Excessive use
- Inappropriate drug administration
- Suboptimal dosing

Collateral damage
- Selection of drug-resistant organisms
- Infection with MDR pathogens
- Super-infection with fungal pathogens
- CDI

CDI, *Clostridium difficile* infection
Use of most classes of antibiotics has been associated with CRE carriage or infection

- Exposure to antibiotics are amongst the most prominent risk factors for CRE but findings implicating specific antibiotics have been diverse across published studies

- Multiple antibiotic classes have been identified as possible risk Fx for colonization or infection with CRE including the:
  - Carbapenems
  - Cephalosporins
  - Fluoroquinolones
  - Beta-lactam/beta-lactamase inhibitors
  - etc

Prior carbapenem therapy is not a prerequisite for acquisition for CRE

• Several studies have shown that prior carbapenem therapy is not a prerequisite for acquisition.

• Point prevalence survey of asymptomatic carriage of Klebsiella pneumoniae carbapenemase: 5.4% patients were carriers and only 18% of them were treated with any carbapenem prior to the survey.

• The genes conferring such resistance usually reside on large plasmids, which frequently carry additional resistance determinants that confer cross-resistance to several classes incl the fluoroquinolones and aminoglycosides.

Brink et al. J Clin Micro 2012;50:525-527
Weiner-ell et al. J Hospital Infection 2010;74:344-349
What makes CRE genes special?

- Spreads at an unprecedented rate
- Also in the community – not limited to healthcare contact
- The plasmid on which it occurs, is a broad host range IncL/M type
  - Thus can spread between Enterobacteriaceae, as well as Gram negative non-fermenters e.g. *A. baumannii*
- The plasmid, pEL60, is found in a plant pathogen, *E. amylovora* originating from pear, apple and quince in Lebanon
- On the plasmid, the NDM-1 gene is surrounded by other mobile resistance mechanisms
- Plasmid also carries the *mucAB* genes, conferring UV light resistance → plasmid can survive in the environment
- Not only is the plasmid mobile, but the NDM-1 gene is on a mobile element, an insertion sequence, and can jump between plasmids as well

Multiple resistance genes
  - e.g KPC or NDM +
  - Fluoroquinolone R gene +
  - Aminoglycoside R gene +
  - Antibiotic efflux pumps
pNDM-HK Encoding NDM-1

Figure 1. An overview of the blaNDM-1 encoding plasmid, pNDM-HK. Starting from the outside, the first circle indicates the coordinate of the complete plasmid circle and the 28.9 kb variable region is showed in red. The open reading frames (ORFs) were annotated in the second circle with arrows representing the direction of transcription. Coding sequences with and without pLL60 homologs are indicated in grey and black, respectively. All IS26 elements are indicated in green. The variable resistant region is coded by the same color scheme as in figure 2. The third circle indicates the functional sequence blocks. The G+C plot is indicated in the inner circle (mean 51.5%), ranging from high (grey) to low (black).

doi:10.1371/journal.pone.0017989.g001

Plos ONE March 2011; 6(3) e17989
Prior carbapenem therapy is not a prerequisite for acquisition

- New Delhi Metallo-b-lactamase (NDM) readily hydrolyzes all penicillins, all cephalosporins, and carbapenems (with the exception of aztreonam) but is on a large 180-kb resistance-conferring genetic element that contains a variety of other resistance determinants, including:
  - a gene encoding another broad-spectrum beta-lactamase (CMY-4)
  - and genes inactivating erythromycin, ciprofloxacin, rifampicin, and chloramphenicol.
  - In addition, the genetic element encodes an efflux pump capable of causing additional antimicrobial resistance.

- As a consequence, prior use of any of these antibiotic classes may select for carbapenemase-producing GNB.

Brink et al. J Clin Micro 2012;50:525-527
Weiner-ell et al. J Hospital Infection 2010;74:344-349
Therefore an overall decrease in antibiotic use is recommended

• Besides the extensive drug resistant (XDR) nature of the CRE genes, the role of formulary interventions in controlling CRE is not well studied

• Therefore, rather than targeting a specific class or limiting specific agents, overall reduction in antibiotic use is recommended as a focus for ASPs.

• A patient’s cumulative antibiotic exposure history is likely to be more important than any one specific exposure when determining the likelihood of developing a CRE infection

In this 4-year case-control study (n=102), the only covariate independently associated with CRE in all multivariate analysis was the cumulative number of prior exposures. Compared with controls, the odds ratios (95% confidence interval) were 1.43 (1.19–1.72), 2.05 (1.70–2.47), and 2.93 (2.43–3.53) for 1, 2 and ≥3 antibiotic exposures, respectively.

• It also appears that not only is prior cumulative exposure a risk factor, but that the risk increases with increasing duration of prior treatment.

• Kritsotakis et al recently demonstrated that this was the case for β-lactam/β-lactamase inhibitor combinations [odds ratio (OR) 1.15 per day increase; \( P=0.001 \)] and also for the fluoroquinolones, where increased duration of treatment amplified the effect of exposure to carbapenems (and vice versa) (OR 1.02 for interaction term, \( P=0.0009 \))
Risk factors for CRE acquisition or infection in South Africa:
2nd. Role of invasive devices
Role of invasive devices in colonization or infection due to CRE

- CR *Enterobacter* species: in multivariate analysis, a high invasive-device score remained a predictor of such CRE (p=0.02)

- Similar significance seen for KPC-producing *K. pneumoniae*
  - CVP (OR 5.22;95%CI 2.38-11.46; P<0.001)
  - Urinary catheter (OR 7.53;95%CI 3.49-16.26; P<0.001)

- Limiting use of invasive devices and taking appropriate care if used (i.e urinary catheter care-bundle) might potentially be an NB intervention

Summary of strategy to prevent emergence and spread of CRE

- Rectal screening of all foreign pts upon admission including pts transferred from local hospitals and/or known to have had a CRE

- Overall decrease in antibiotic use of all classes

- Shorten duration of antibiotic therapy

- Limiting use of invasive devices and taking appropriate care with a “care-bundle” approach (i.e. urinary catheter care-bundle)
Step 4

Present results of ASP projects to the clinicians/medical staff
Pilot study in a 25 bed level 1 TICU + 10 bed BICU

PDR *A.baumannii* & *P.aeruginosa* defined as susceptibility to colistin alone

Daily clinical ASP rounds

Brink AJ et al. (Unpublished)
Prospective audit
Daily antibiotic rounds by clinical pharmacologist based on survey of practices

- 1. Empiric therapy without microbiological specimens
  - Cultures

- 2. Inappropriate agent choices
  - a- Duplicate spectrum
  - Duplicate spectrum
  - b- Inappropriate combinations
  - ≥4 agents

- 3rd. Failure to de-escalate- from broad-narrow spectrum

- 4th. Excessive duration treatment
  - ≥10-14 days

- 5th. Inappropriate prophylaxis (agent/timing/duration)
  - >24 hrs
## Impact of prospective audit of antimicrobial use

<table>
<thead>
<tr>
<th></th>
<th>Admissions in ICU</th>
<th>No of PanMDR Acinetobacter Infections</th>
<th>Admissions in ICU</th>
<th>No of PanMDR Acinetobacter Infections</th>
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<tr>
<td></td>
<td>2009</td>
<td>2009</td>
<td>2010</td>
<td>2010</td>
</tr>
<tr>
<td><strong>Jan</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Feb</strong></td>
<td>81</td>
<td>6</td>
<td>95 ***</td>
<td>0</td>
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<tr>
<td><strong>March</strong></td>
<td>80</td>
<td>6</td>
<td>77</td>
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<tr>
<td><strong>April</strong></td>
<td>62</td>
<td>3</td>
<td>70</td>
<td>1</td>
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<tr>
<td><strong>May</strong></td>
<td>91</td>
<td>0</td>
<td>51</td>
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<tr>
<td><strong>June</strong></td>
<td>76</td>
<td>8</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>390</td>
<td>23</td>
<td>355</td>
<td>6</td>
</tr>
</tbody>
</table>

- Significantly less PDR infections 1.69% (6/355 patients) vs 5.89% (23/390) after active intervention (P=0.0004)

Brink AJ et al. (Submitted for publication)
Conclusions
The global spread of ESBLs & CRE is worrisome given the frequency with which *Enterobacteriaceae* cause infections and the high mortality reported with infections due to such pathogens.

The goal of antibiotic stewardship programs (ASPs):

- To promote the appropriate use of antimicrobials
  - The right selection, duration, dose, timing and route of administration
- To improve clinical outcomes
  - By reducing the emergence of resistance
  - By limiting drug-related adverse events
  - By minimizing the risk of unintentional consequences
    - eg, *Clostridium difficile* infection
Conclusion

• Practically, tools to get started with an ASP

  • Step 1: Develop an interdisciplinary team and define the roles and responsibilities of team members

  • NB. Step 2: Do a survey of current practices

  • Step 3: Select strategies by which to execute an ASP

  • Step 4: Present results of ASP projects to the clinicians/medical staff