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Research Article

Species Distribution and Susceptibilities of Bacteraemic Isolates from a United Kingdom Level 3 Neonatal Intensive Care Unit, a 5 Year Experience

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Abstract

Empirical antimicrobial guidelines are constantly evolving in response to laboratory susceptibility data. Broad spectrum agents exert a selection pressure gradually increasing antimicrobial resistance over time. In the level 3 neonatal intensive care unit (NICU), the majority of blood culture isolates are coagulase negative staphylococci (CoNS), which require appropriate empirical therapy.

To assess antimicrobial resistance trends of CoNS and other commonly isolated organisms over a five year period in a busy neonatal unit.

A retrospective analysis of all laboratory positive neonatal blood cultures from January 2005 to October 2010 was undertaken, recording species and susceptibility data.

During the 5 year period 794 positive blood cultures were identified, with 639 isolates (80.5%) identified as CoNS. The remaining 155 included 34 other Gram positives (4.3%) and 121 Gram negatives (16.5%). There is an increase in CoNS resistance over 5 years to cloxacillin with no resistance to vancomycin identified. Gram negative resistance patterns appear more stable, with a decreasing resistance to amoxicillin reflecting changes in prescribing policies.

Changing local trends in antimicrobial susceptibility should be considered when formulating empiric antimicrobial policies.

Keywords: Neonatal, sepsis, bacteraemia, coagulase negative staphylococci.

Introduction

Survival rates amongst patients admitted to neonatal intensive care units (NICU) has increased significantly over the last ten years. One of the commonest interventions in patients admitted to NICUs is the initiation of antibiotics for the management of sepsis. Whilst there has been little change in the epidemiology of organisms associated with early onset sepsis (less than 72 hours), there has been increasing interest in the incidence and clinical relevance of coagulase negative staphylococci (CoNS). These organisms have the potential for pathogenicity in the neonates, the reasons for this include prematurity of the immune system, predisposing antibiotic consumption as well as the placement of intravascular catheters. The management of sepsis in NICUs is complex. There is a paucity of evidence based

guidelines for the prescription of antimicrobials in children compared to the adult population, which results in a wide variation of guidelines between NICUs, often based on local experience and anecdotal evidence. Increasing levels of resistance in Gram negative organisms globally, as well as noticeable increases in the minimum inhibitory concentrations (MICs) of Gram positive organisms have specific implications in neonates. We aimed to look at isolates recovered from blood cultures, taken as part of routine clinical care to identify trends in resistance and map this to antimicrobial consumption in the unit over the last 5 years.

Methods

The NICU contains 6 intensive care cots and 6 high dependency cots alongside 22 special care cots. On average 7000 deliveries are managed by the unit each year, of a total of 11,500 deliveries across the Trust.

The hospital pathology system was queried for all blood cultures (irrespective of significance) between January 2005 and October 2010. Susceptibilities of isolates were downloaded for all CoNS and the Gram negatives that were associated with clinical signs of sepsis. Antimicrobial susceptibilities, including Gram negative resistances, were measured by automated methods, using with Vitek 2 system (Biomerieux, France) and reported according to the European Committee on Antimicrobial Susceptibility Testing

(EUCAST) breakpoints. Consumption data for antibiotics (in terms of vials) were obtained from the pharmacy department, and based on the number of vials delivered to the unit. Individual medical notes and drug charts were not reviewed, but each blood sample was taken on clinical suspicion of sepsis, as per unit protocol. Data was analysed using Microsoft® Excel 2010 pivot tables.

Results

From January 2005 to October 2010, there were 794 positive blood cultures, of which 639 (80.5%) were identified as CoNS by routine laboratory methods. The remaining 155 included 34 (4.3%) other Gram positives (4 *Staphylococcus aureus*, 10 *Streptococcus agalactiae* and 20 alpha haemolytic streptococci)

and 121 (16.5%) Gram negative organisms (120 Enterobacteriaceae and one *Pseudomonas* aeruginosa). Susceptibilities for Enterobacteraciae were unchanged over the study period, although a reduction in ampicillin resistance was noted. The susceptibilities that were analysed for CoNS were cloxacillin (CLX), ciprofloxacin (CIP), erythromycin (ERY), fusidic acid (FUS) and trimethoprim (TM). Best fit analyses were also plotted on the same graph (Fig 1). Vancomycin MICs were not performed routinely in the laboratory. Consumption data was generated from dispensary records in the pharmacy. Numbers of vials on each antibiotic was plotted (Fig 2). There are no WHO definitions for the defined daily dose (DDD)of antibiotics in neonates, and thus the numbers of vials was used as a rough guide of consumption data The 2011 consumption data in figure 2 only includes the first eight months of that calendar year.

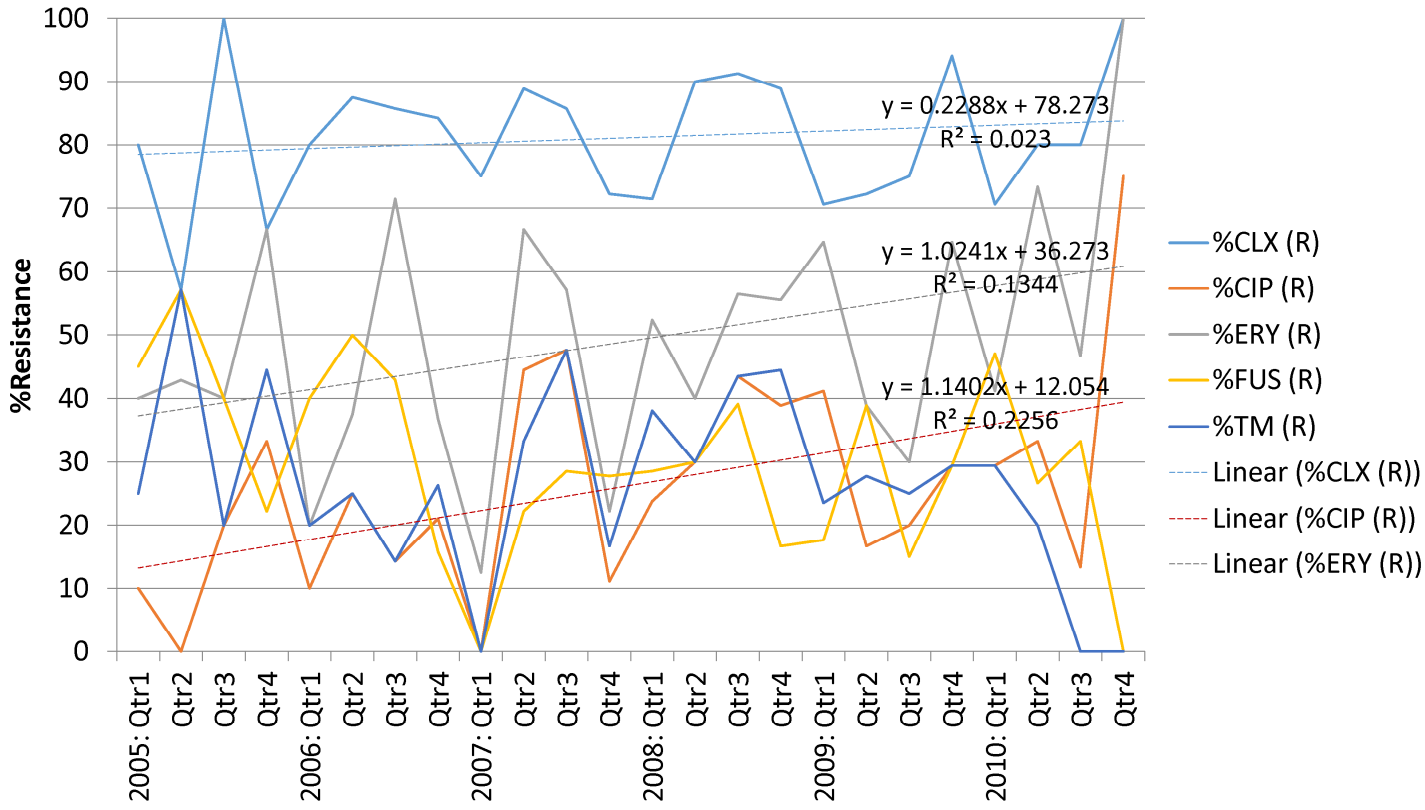

Figure 1: Resistance Patterns amongst Coagulase Negative Staphylococci 2005-2010. Key: CLX=Cloxacillin, CIP=Ciprofloxacin, ERY=Erythromycin; FUS=Fusidic Acid; TM=Trimethoprim

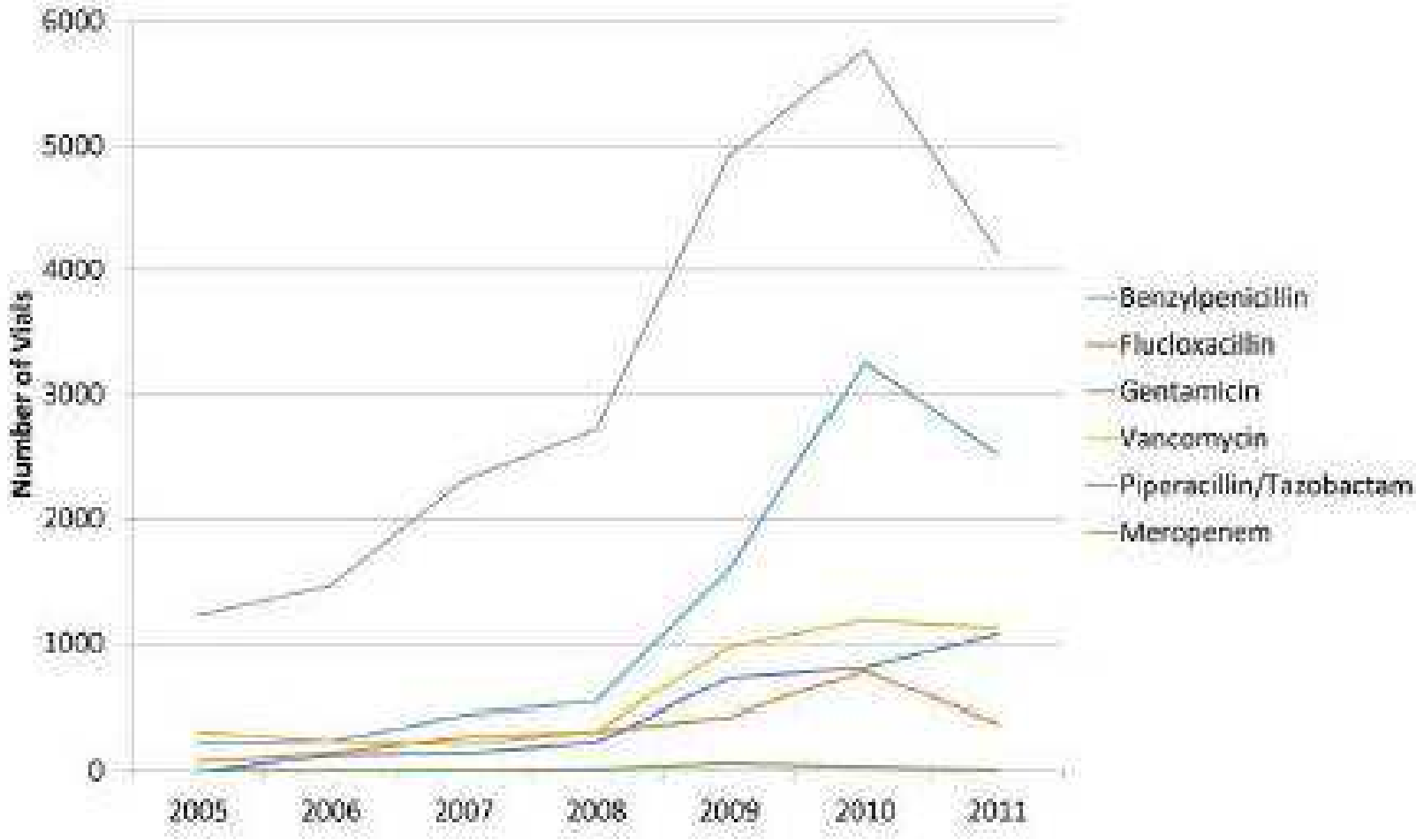

Figure 2: Consumption of Antibiotic Vials in NICU 2005-2010

Discussion

Antimicrobial stewardship is an evidence based strategy to manage the emergence of increasingly resistant organisms through prudent prescribing. The focus on delivery of such programmes has increased over the last few years as noted by Bal et al (2011), with particular emphasis on the role of broad spectrum antibiotics and de-escalation. At the heart of the delivery of these new methodologies is a seamless interface between the laboratory susceptibility data, the medical microbiologist and the clinician.

Our data has demonstrated a high level of resistance to cloxacillin in all of our CoNS isolates, with a slow increase in this level over time. Whilst this trend is not statistically significant ($p>0.05$) and

could be attributable to statistical variability, the suggestion is that β-lactams are no longer appropriate in the empirical antimicrobial management of neonates in whom a CoNS is suspected to be significant. An increase in this resistance is in part due to the increasing use of β-lactams as first and second line agents in neonatal sepsis. This would suggest a more prominent role for glycopeptides as empiric agents when clinical sepsis is suspected. The use of techniques for the standardisation of blood sampling aim to reduce contamination rates, although early cessation of therapy is recommended if the blood culture result is deemed a contaminant.Marques-Minana et al (2010) noted that the use of glycopeptides in neonates is complicated by unpredictable pharmacokinetics, a narrow therapeutic window, and confusion about appropriate dosing regimens. Often therapeutic ranges of 10-20 mg/L for vancomycin are quoted (as

in our unit), but these are difficult to achieve, resulting in sub-optimal therapy. For those children with bacteraemias due to meticillin-resistant *S. aureus* (MRSA), Hussain et al (2011) demonstrated that lipopeptides have been successfully used guided by therapeutic drug monitoring.

Stuart et al (2011) noted that whilst CoNS are emerging as important nosocomial pathogens, large scale studies confirm a heterogenity of species and wide ranges in vancomycinsusceptibility. This has not been reflected in clinical practice where identification and quantitative susceptibility testing is not performed routinely on significant CoNS isolates. The study by Moise at al (2009) concluded that higher vancomycin minimum inhibitory concentrations (MICs) are associated with poorer outcomes for *Staphylococcus*

*aureus*bacteraemiaes (SAB), but no such studies have been performed on CoNS. There has been some discussion in the UK of adopting a clinical breakpoint of vancomycin of 1 mg/L for SAB, resulting in more usage of lipopeptides and oxazolidonones. Further studies should be performed to assess this practice in significant CoNSbacteraemias.

Changes in antimicrobial prescribing should be driven in part by a retrospective analysis of prescribing and consumption. The reduction in amoxicillin resistance in enterobacteraiace is driven in part by the use of aminoglycosides for the management of gram negative sepsis, which was stable practice over the study period. Our figures reflect consumption of vials on the NICU, but this cannot be standardised due to differing manufacturers and changes in administration practices over time. Our figures do

suggest a large increase in consumption since 2008, the cause of which would require further investigation. The lack of WHO defined DDD's prevents us from drawing comparisons with other centres, although Liem et al (2010) have made attempts to draw up DDDs. These have not been standardised due to the wide variation of weights in the neonatal population. It is essential for units to monitor their antimicrobial resistance rates and consumption to inform future empirical and management guidelines.

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