The Epidemiology of Candidaemia in Northern Ireland 2001-2011

November 2013

Executive Summary

In Northern Ireland (NI), over the last decade, the analysis of trends from voluntarily reported laboratory data has shown a rise in the number of candidaemias reported. In addition, rates of candidaemia in NI have been consistently higher than those reported from England and Wales,

Epidemiological studies have shown that between 28 and 47% of Candida bloodstream infections occur in high risk patients. The prevalence of candidaemia infections is concerning as infection is associated with longer hospital stay and significant mortality which can be up to 71%[4–6].

This audit aimed to improve our understanding of the epidemiology, laboratory diagnostic methods and clinical significance of candidaemia in Northern Ireland using a number of different methods. It showed that an increasing number of Candida isolates have been reported over the past 10 years. As expected, *C.albicans* represented the largest proportion of cases. Voluntary reporting to the PHA was high, with 95.6% of all isolates reported over the 10 year period. Approximately 94% of these were speciated.

Similar to the epidemiology of these infections in England and Wales, during 2011, rates of candidaemia tended to be higher in the older, male population and those under the age of 1. The majority of infections occurred in hospital inpatients (90.9%).

From 2007-2011, 51.2% (233/455) of Candida isolates underwent sensitivity testing. Almost all *C. albicans* were sensitive to all antifungals tested, with the exception of a single case of 5flucytosine resistance. Over the 5 year period, a higher proportion of resistance to fluconazole was reported in *C. glabrata*.

Laboratory diagnostic methods throughout NI and England were broadly similar. All laboratories surveyed used one of two commercial blood culture systems, followed by subculture in conditions that would support the growth of candida species.

A review of candidaemia patients during 2011 revealed a relatively high mortality, for those where data was available, at 35.1%. A review of the management of the cases showed that the majority of patients did not undergo fundoscopy during their stay and less than 20% had an echocardiograph after a positive result for Candida.

The audit also revealed that CVC removal was generally not well recorded in the patient notes, which is important for patient management.

As a result of these findings a number of priorities were identified including: raising the awareness of existing and more recent guidelines for improving the management of Candidaemia infections; sharing information on daily review proformas in ICU to improve recording of patient notes; encouraging more antifungal sensitivity testing in laboratories and; circulating DH CVC Care Bundle to highlight recording information for CVC removal.

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1.0 Background

Healthcare associated infections (HCAIs) occur both in the hospital and community setting following a health care intervention. HCAIs have received significant attention over the last decade due to the associated patient morbidity and mortality and the burden on the health service. Most infection prevention and control activity has been focussed on two HCAIs; meticillin resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*. A zero tolerance approach has been effective for achieving significant reductions in these infections and has been observed throughout the UK. Despite this, the prevalence of other HCAIs, such as invasive fungal disease has remained a burden in the healthcare setting.

Fungi have emerged as an important cause of nosocomial infection with the majority of infections being caused by *Candida* species. These organisms are present in a variety of clinical specimens and can cause conditions ranging from superficial colonisation, which is not a problem in itself, to life-threatening blood stream infections (candidaemia).There has been a worldwide increase in the incidence of candidaemia[1,2] which has been attributed to the increasing complexity of surgical procedures, more high risk patient populations and changes to hospital patient demographics. The advent of new surgical techniques and advances in critical care medicine mean that patients are now living longer and invasive surgical procedures are being offered to more patients who have significant co-morbidities. There has also been an increase in: more invasive procedures, the use of intravenous catheters and implantable prosthetic devices; total parenteral nutrition (TPN), renal replacement therapy and the use of broad spectrum antimicrobial therapy and immunosuppressants as well as an increase in the number of neutropenic patients following chemotherapy. Collectively, these changes increase the risk of developing a *Candida* bloodstream infection (BSI).[3,4]

Epidemiological studies have shown that between 28% and 47% of *Candida* bloodstream infections occur in high risk patients who possess one or more of the characteristics described above.[3] The prevalence of candidaemia infections is concerning as infection is associated with longer hospital stay and significant mortality which can be up to 71%[4–6], depending on the patient population. *Candida* species also appear to be evolving epidemiologically, with a rise in non-*albicans* species (e.g. *Candida krusei* and *Candida*

glabrata) that have reduced susceptibility to fluconazole, the most commonly used antifungal agent.[7]

In Northern Ireland, there has been an on-going commitment to tackle the challenges of healthcare-associated infections, reflected in the strategic regional action plan "Changing the Culture 2010".[8] This has resulted in significant reductions in infections such as MRSA and *C. difficile* over the last decade. However, for the same time period, the analysis of trends from voluntarily reported laboratory data has shown a rise in the number of candidaemias reported. In addition, rates of candidaemia in Northern Ireland have been consistently higher than those reported from England and Wales, with Health Protection Agency data for 2010 indicating a twofold difference.[9] This variance is concerning given the patient implications and the impact on the health service. Estimates from a case control study[10] applied to the total number of candidaemias in NI during 2010 (113 episodes) suggest that up to 39 deaths may have been attributable to candidaemia with an estimated hospital cost of care of at least £935,000.

In the absence of mandatory reporting and without a dedicated surveillance programme for candidaemia, a different approach is required to investigate why rates in NI are so high compared to England and Wales. We hypothesise that this may relate to candidaemia diagnosis, reporting or the case mix of patients in NI. For example, if laboratory techniques in NI were better at confirming candidaemia, when compared to laboratories in England, this would account for a higher number of cases identified. Alternatively, it may be that reporting is better locally so that the ascertainment of cases is higher. It may also be possible that the prevalence of known risk factors for candidaemia may be higher in the NI population.

This audit will use candidaemia management standards and guidelines produced by the British Society for Medical Mycology (BSMM)[11], the Health Protection Agency[13] (now PHE) laboratory diagnostic guidelines and the Infectious Disease Society of America (IDSA)[12]. Together, they assess aspects of antifungal choice, dose, duration of therapy and management strategies including the removal of central venous catheters and fundoscopy following candidaemia identification.

1.1 Aim and objectives

To improve our understanding of the epidemiology, laboratory diagnostic methods and clinical significance of candidaemia in Northern Ireland.

The main objectives were:

1 To compare laboratory diagnostic methods in NI and England.
2 To validate voluntary candidaemia data against laboratory records and assess the degree of speciation.
3 To describe the case mix profile of candidaemia patients in NI in the context of known risk factors.
4 To explore the management of candidaemia patients using known standards.

1.2 Standards

This report will reflect on a series of standards applicable to *Candida* species infection proposed by Public Health England (formally the Health Protection Agency), the British Society for Medical Mycology and the Department of Health (UK) as described below.

S1 All invasive *Candida* spp infections to be reported to the Public Health Agency[13]

S2 All fungi obtained from sterile sites should be identified to species level[11]

S3 All patients with candidaemia should have central venous catheters removed or replaced within maximum 48 hours of *Candida* spp being identified in a blood culture[11]

S4 All patients with candidaemia should be treated with a systemic antifungal agent at an appropriate dose, and breakthrough fungaemia treated with an alternative agent[11]

S5 Practice and procedures that improve the quality of blood culture investigations should be implemented[14]

1.3 Data Source

1027 positive cultures for *Candida* sp from 2001-2011 were identified through the Public Health Agency's regional database for the voluntary reporting of *Candida*. All laboratories in Northern Ireland participated in the laboratory method survey. For the 2011 patient case review, 83 of 98 (85%) charts were retrieved from hospital patient record departments.

2.0 Methodology

2.1 Project Design

To address the 5 standards the audit used a three-pronged approach:

1. The completeness of reporting to the PHA was assessed by carrying out a validation study comparing candidaemia isolates reported to the PHA to what was known in the laboratory (S1, S2, S5). Antifungal sensitivity was also investigated.
2. Laboratory diagnostic methods were investigated to assess standardisation and comparability across the region (S5). To assess methodological differences a comparison was also made with European Antimicrobial Surveillance Network (EARS-net) laboratories in England.
3. The case mix, risk factors and treatment of individuals with candidaemia were reviewed using patient notes from cases identified during 2011 (S3, S4).

2.1.1 Laboratory data validation

To investigate the proportion of invasive candidaemia infections that are reported (S1), voluntarily, to the PHA, isolates of *Candida* from all clinical microbiology laboratories in Northern Ireland from 2002-2011 were extracted from a regional database. This list was sent to each laboratory for validation against their own records. The dataset contained basic demographic information about the patient, including their location at the time the specimen was taken. The location was categorised into inpatient, outpatient, GP, A&E or unknown. This dataset was also used to determine what proportion of *Candida* isolates were speciated (S2). Antifungal sensitivity data for the period 2006–2011 was also requested from laboratories to determine resistance patterns for different *Candida* species. The number of candidaemias reported as a proportion of the total number of blood culture requests was determined for all the laboratories in Northern Ireland. Further, to investigate the variation in total blood culture requests, the number of bed days per blood culture requests was determined for the period 2009–2011 (S5). Comparative data on the latter two aspects was also requested from PHE for laboratories in England. All data were analysed using Microsoft Excel.

2.1.2 Laboratory Methods

All hospital microbiology laboratories in NI were asked to complete a questionnaire about their diagnostic methods including information on clinical guidelines, blood culture methods (S5), isolation procedures, sensitivity testing and reporting (see Appendix 1). As each laboratory serves one Trust, they were asked if there were any local guidelines to determine when blood cultures for candidaemia should be taken. Responses were collected via telephone. The same questionnaire was distributed to ECDC EARS-Net laboratories in England (n=24). Formic Web forms were used to collect this information and the questionnaire was designed as a web form which was shared with laboratories via an email containing a URL to the form.

2.1.3 Case Review

Approval was gained from the Trusts prior to commencing the case reviews and included all individuals with a laboratory confirmed *Candida* isolate during the period January 1st 2011 to December 31st 2011(n=98). To ensure consistency in reviewing the case notes, one Microbiology registrar completed this aspect with the help of the Surveillance Coordinator who assisted with collating the demographic and patient journey information for the proformas. A clinical proforma was designed to assist with data collection using risk factors determined from a literature review and following consultation with clinicians on the Steering Group (see Appendix 2). Information gathered included patient age and sex, clinical history, underlying risk factors such as use of TPN, steroids, immunosuppressants and co-morbidities, information on central venous catheters (CVC), peripherally inserted central catheters (PICC), prescribing and microbiology data (S3 and S4).

After piloting the proforma in one of the Trusts it was amended following agreement with the steering group. Thirty day mortality data was calculated by retrieving dates of death from the HSC Business Services Organisation (BSO) using the health and care numbers from the original 2011 validated database.

To assist with data entry, a questionnaire was designed using EpiData software (Version 3.1 The EpiData Association, Odense Denmark, 2003-2004). Appropriate validation and consistency checks were used to reduce the number of transcription errors. The complete dataset was exported to IBM SPSS Version 19.0 for analysis. Data were further quality checked using validation routines.

3.0 Findings

3.1 Laboratory data validation

In total, 95.6% of isolates were reported to the PHA under the existing voluntary reporting scheme (1027/1074). An analysis of these data, to examine the proportion of all isolates reported and speciated prior to and post BSMM guidelines[11], revealed no systematic differences (see Appendix 4). Of the validated candidaemia isolates, *Candida albicans* was the most common over the ten year period, accounting for 53.1% of reports. Other prevalent species included *C. glabrata* (22.9%) and *C. parapsilosis* (9.5%; Table 1). This is epidemiologically similar to the overall England, Wales and NI data from the last 4 years, published by Public Health England (formally HPA).[15]

Table 1: Total number and proportion of Candida species reported to the Public Health Agency from 2002 – 2011

Species	Total	%
Candida albicans	547	53.3
Candida glabrata	236	22.9
Candida parapsilosis	98	9.5
Candida tropicalis	45	4.4
Candida other named	12	1.2
Candida lusitaniae	11	1.1
Candida guilliermondii	9	0.9
Candida krusei	8	0.8
Candida famata	6	0.6
Candida dubliniensis	5	0.5
Candida kefyr	4	0.4
Candida lipolytica	1	0.1
Candida sp	45	4.4
	1027*	

*data reported to PHA only

Non-albicans species accounted for just under half of all Candida isolates each year from 2002 to 2011. Although the occurrence of non-albicans species was slightly more frequent in 2010 (65 cases out of 117) (Figure 1).

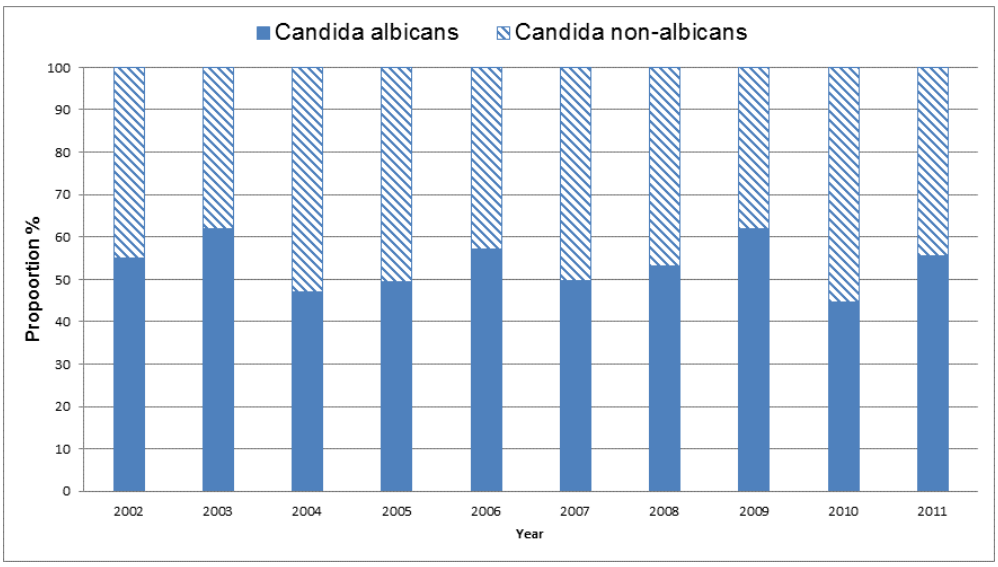

Figure 1 Proportion of Candida albicans and non-albicans species reported to the Public Health Agency Northern Ireland from 2002-2011

3.1.1 Trend analysis

Between 2002–2008, assuming a linear trend, there was an average 9% year on year increase in the rate of candidaemia (incidence rate ratio 1.09 95% CI 1.05 – 1.13) (Figure 2). In absolute terms, this is an increase from 80 episodes in 2002 (4.72 episodes /100,000 population) to 131 episodes in 2011 (7.38/100,000 population). Since 2008, the rate of candidaemia has fluctuated between 5 and 7 episodes per 100,000 population (Figure 2). Despite the slight reduction in candidaemia rates since 2008, during 2011 rates in NI were still statistically higher than those reported from England and Wales[16] (Figure 3).

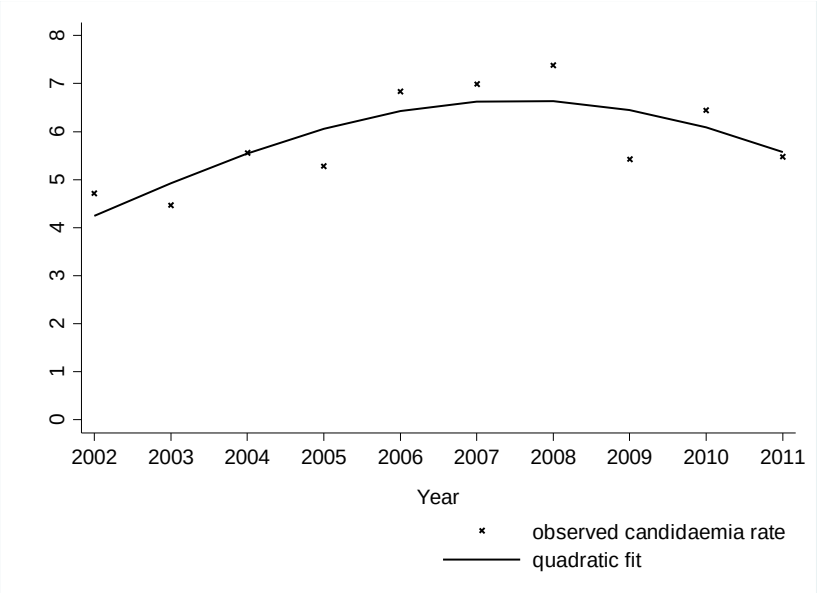

Figure 2 Rate of candidaemia per 100,000 population*, Northern Ireland, 2002 to 2011.

*Population = NISRA midyear estimates for the years 2002 – 2011

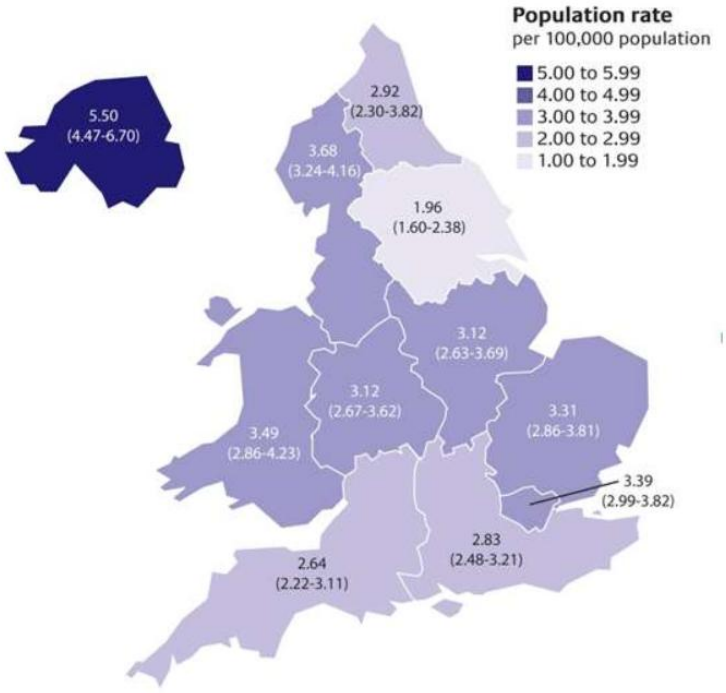

Figure 3 Region specific-rates (95% CI) of candidaemia (extracted from the 2011 Health Protection Agency health protection weekly report)[16]

3.1.2 Age – specific rates

In 2011, rates of candidaemia tended to be higher in the 75+, male population (40 episodes per 100,000 population), with males under the age of 1 also having a higher rate than females (23/100,000; Figure 4). This is similar to the epidemiology of these infections in England and Wales. However, there is a notable absence of candidaemia infections in females less than 14 years in NI when compared to the combined data for England, Wales and NI (Figure 9; Appendix 3).

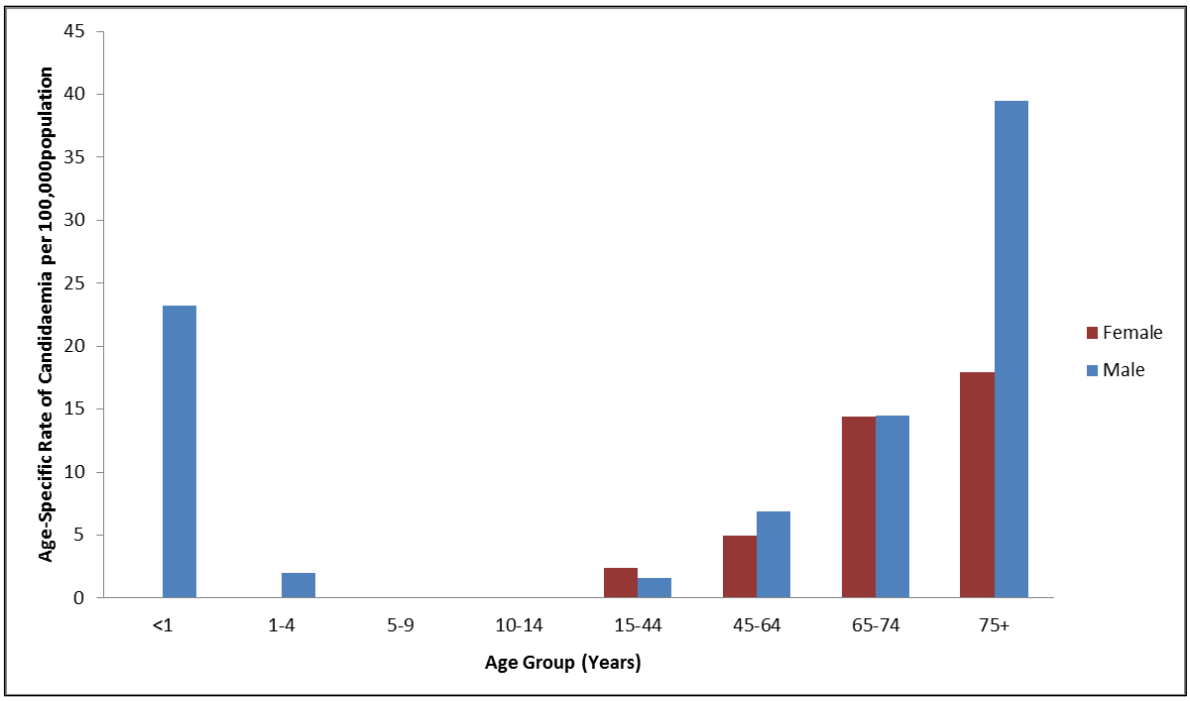

Figure 4 Age-specific rates of candidaemia per 100,000 population in Northern Ireland, 2011 (using 2011 Census population data; see Appendix 4 for raw data).

3.1.3 Patient location at the time the specimen was taken

During 2011, the majority of candidaemias were detected in hospital inpatients (90.9%; Table 2). It was not possible to identify those who developed the infection within two days of admission, and who therefore may have been infected/colonised prior to their hospital stay. It is also not known if the use of the 2 day rule is appropriate in the fungal setting. Previous healthcare contacts were also unknown.

Table 2 The distribution of candidaemia reports by patient source during 2011.

Source Description	Total number	Proportion of all candidaemias (%)
Hospital Inpatient	90	91.8
Hospital A&E	2	2.0
Hospital Outpatient	1	1.0
Unknown	5	5.1

3.1.4 Lab specific data

The number of candidaemias per 1000 blood culture requests (obtained from EARs response) ranged from 1.22/1000 blood culture requests to 2.22/1000 blood culture requests in 2011. As the size of the trust increased (in terms of total occupied bed days for 2011) the number of blood cultures taken increased proportionally. One laboratory had the highest rate of candidaemia per 1000 blood cultures despite having the second lowest number of blood cultures taken. Excluding this laboratory, generally the rate of candidaemia increased with increasing bed days and increased blood culture testing (Figure 5; see Appendix 4 for raw data).

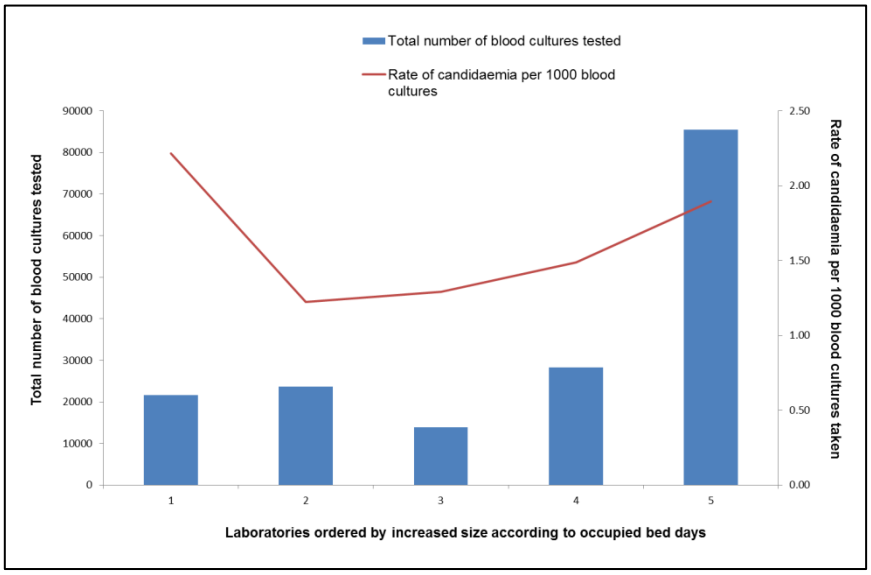

Figure 5 The number of blood cultures tested, presented by increasing occupied bed days status, and the rate of candidaemia per 1000 blood cultures taken during 2009-2011.

The variation in blood culture requests between laboratories, according to the number of bed days showed that one laboratory, with the lowest number of blood culture tests despite having the third highest occupied bed days in 2011, had the highest number of bed days per blood culture (52.9 bed days/blood culture). A second laboratory (laboratory 5), which performed the highest number of blood culture tests, had the lowest number of bed

days per blood culture (21.8 bed days/blood culture) suggesting that this laboratory had a higher rate of blood cultures taken. As data are not presented by hospital, this variation could be down to case mix throughout the trusts. Comparative data were obtained for laboratories in England where an average of 22.9 bed days per blood culture were reported (see recommendation S5).

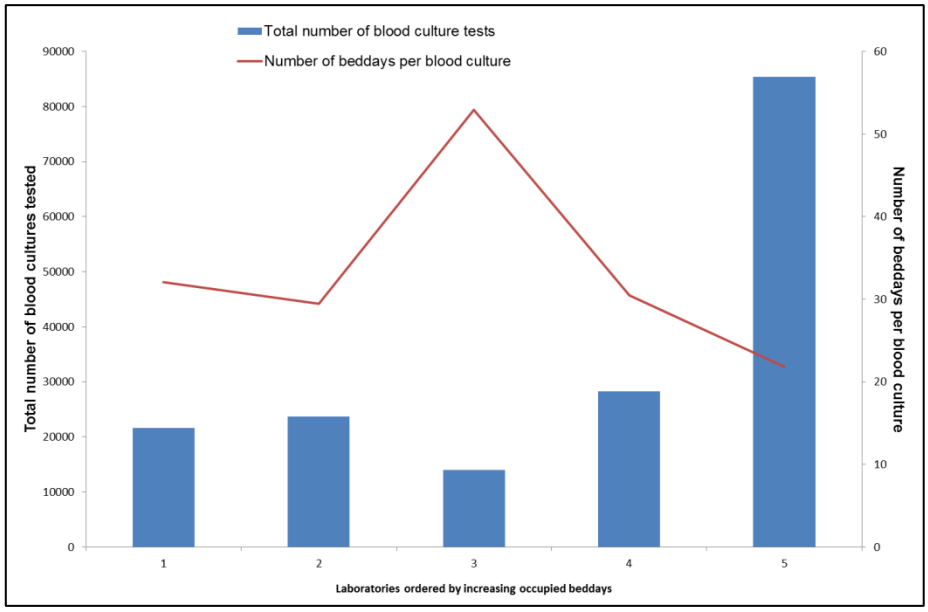

Figure 6 The number of blood cultures taken, by increasing number of occupied beddays, and the number of beddays per blood culture 2009-2011 (see Appendix 4 for raw data*).

3.1.5 Antifungal Sensitivity data

From 2007-2011, 51.2% (233/455) of *Candida* isolates underwent sensitivity testing. Almost all *C. albicans* were sensitive to all antifungals tested, with the exception of a single case of 5flucytosine resistance (Table 3). A similar pattern was observed for *C. parapsilosis*, with 1 case of resistance to caspofungin (Table 3). Over the 5 year period, a higher proportion of resistance to fluconazole was reported in *C. glabrata* (12 out of 78 isolates (15.4%); (Table 3)). However, Figure 7 shows that the proportion resistant has been decreasing over time. Small numbers of resistance to voriconazole were also reported in *C. glabrata* (2 of 46 isolates (4.3%; Table 3). The proportion resistance to voriconazole has fluctuated over time (Figure 8).

Table 3 Resistance to a range of antifungal agents for *C. albicans*, *C. glabrata* and *C. parapsilosis* during the period 2007-2011

Antifungal Agent	*C. albicans*			*C.glabrata*			*C.parapsilosis*		
	Non-susceptible (%)		Tested	Non-susceptible (%)		Tested	Non-susceptible (%)		Tested
AmpB	0	0%	115	0	0%	77	0	0%	19
Fluconazole	0	0%	112	12	15.4%	78	0	0%	20
Voriconazole	0	0%	85	2	4.3%	46	0	0%	13
Caspofungin	0	0%	42	0	0%	16	1	16.7%	6
Nystatin	0	0%	4	0	0%	8	0	0%	0
5Flucytosine	1	1.4%	71	0	0%	61	0	0%	7

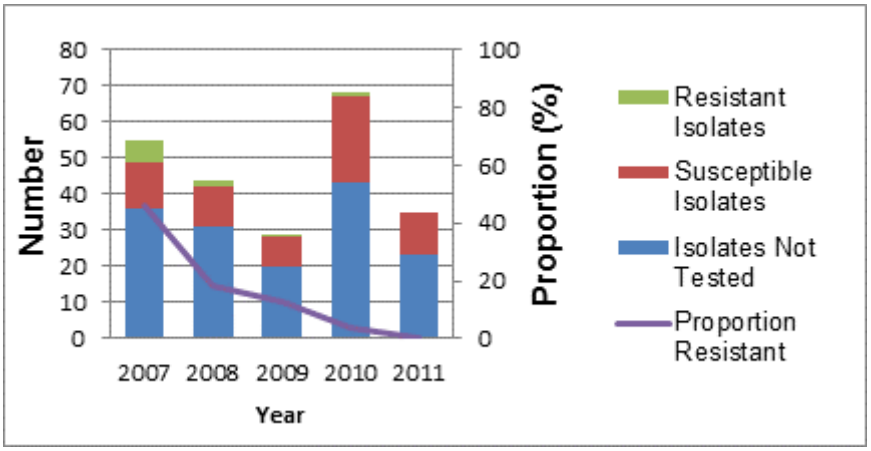

Figure 7 Sensitivity chart showing resistance of *C. glabrata* to Fluconazole from 2007 to 2011.

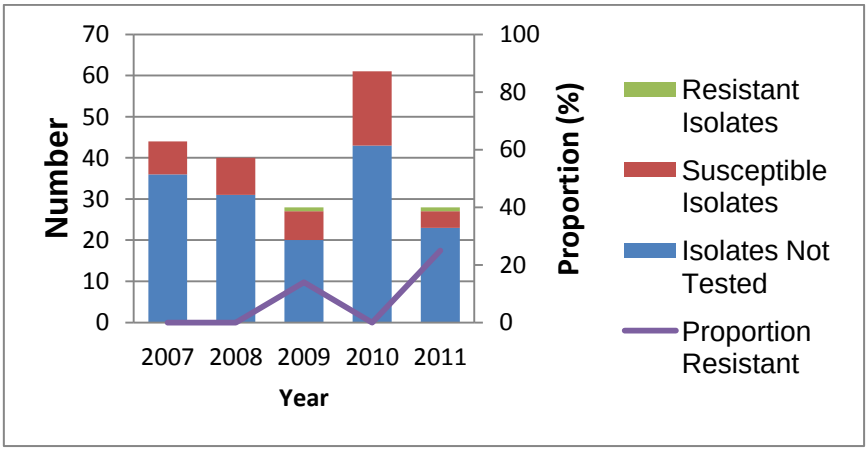

Figure 8 Sensitivity chart showing resistance of *C.glabrata* to Voriconazole from 2007 to 2011.

3.2 Laboratory Methods

3.2.1 Ward practice

All Trust laboratories in Northern Ireland took part in the laboratory methods survey (N=5). They all reported that they gave advice about how to take blood cultures. Trusts are generally not following any rigid protocol as to when blood cultures should be taken and in practice most are taken when patients have fevers and/or rigors or are non-specifically unwell.

In England, four out of the seven responding laboratories reported they did not have clinical guidelines to determine when blood culture for possible candidaemia should be taken. One laboratory reported that they advise that a repeat blood culture should be carried out two days after the first to assess clearance. This lab also advised that antifungal treatment should be given for at least 14 days after the last positive blood culture.

3.2.2 Blood culture methods

In Northern Ireland, two laboratories use the Bactec method and the remaining three use the BacT Alert method. Table 4 summarises the blood culture media routinely used by each laboratory. No laboratories reported using any special procedures such as venting. Tests for *Candida* do not have to be specifically requested by the clinician as all the standard systems in use permit the culture of *Candida* spp.

In England, all laboratories that responded used the BacT Alert system for blood cultures, with standard BacT Alert aerobic and anaerobic media. No laboratories reported using any special procedures such as venting. As in Northern Ireland, tests for *Candida* do not have to be specifically requested by the clinician.

Table 4 Blood culture media routinely used by laboratories in NI.

Laboratory	Standard Aerobic & Anaerobic Bactec bottles	Standard BacT Alert Aerobic and Anaerobic	Special fungal bottles
1		✓	
2		✓	
3	✓		Available but rarely if ever used
4	✓		Used by ICU but seldom elsewhere
5		✓	

3.2.3 Incubation periods for Candida blood cultures

Incubation periods for *Candida* were generally consistent across laboratories in Northern Ireland. In the two laboratories using the Bactec system, standard blood culture bottles were incubated for five days. If special fungal bottles were received, they were incubated for 14 days and if sub-acute bacterial endocarditis (SBE) was suspected the incubation time was 21 days. For the remaining three labs that use the BacT alert method there were slight variations in the incubation period. One site incubates blood cultures for five days unless SBE is suspected in which case it is incubated for 21 days. Another incubates blood cultures for six days unless SBE is suspected in which case they use a 14 day cut off. Finally, a third lab incubates for seven days with a similar 21 day incubation period for suspected cases of SBE. None of the labs performed terminal sub culture.

In contrast, all laboratories that responded in England reported their normal incubation period for BacT Alert was 5 days. Two labs stated if SBE is suspected the incubation time would be 21 days. None of the laboratories performed terminal sub culture.

3.2.4 Candida isolation procedures from positive bottle

Table 5 summarises the media for the sub-culture of a *Candida* positive bottle, the incubation conditions and the incubation period used in laboratories in Northern Ireland. All laboratories sub-culture *Candida* positive bottles onto blood agar with one laboratory using only Sabouraud agar concurrently. Two laboratories culture onto CAN-2 as well as blood agar and two use the three methods simultaneously. The incubation temperature ranges from 35 – 37 ^{0}C and all laboratories except one incubate in air. The incubation period for all laboratories was 24-48 hours.

Table 5 Candida isolate procedures, incubation conditions and incubation period for labs in NI.

Laboratory	Blood Agar	Sabouraud	CAN-2 Chromogenic (BioMerieux)	Temperature* (^{O}C)	Incubation conditions	Incubation period (hours)
1	✓	✓	✓	37	Air	24-48
2	✓		✓	35	Air	24-48
3	✓	✓	✓	37	Air	24-48
4	✓	✓		35	CO_2	24-48
5	✓		✓	37	Air	24-48

*Some unusual *Candida* species and other genera of yeast causing bloodstream infections may grow better at 35 °C than 37 °C

Similarly in England, four laboratories reported positive bottles were sub-cultured to blood agar & Sabouraud media, with three labs reporting they sub-culture on to CAN-2 medium. The incubation temperature ranges from 35 – 37 °C in all laboratories for 24-48 hours, aside from one laboratory that incubates sub-cultures for 10 days. Three laboratories stated they would extend incubation if yeasts were seen in the Gram stain or there was no growth. Two of these laboratories also incubate a duplicate set of plates at 30°C.

3.2.5 Candida speciation

All labs in NI reported that they identify *Candida* to species level. Four labs used the VITEK method with one lab using API 32C. This latter method was used in another lab if the VITEK was inconclusive.

In contrast, three laboratories in England stated they identify all *Candida* to species level using the MALDI-TOF system with one of these also using API 32C and another using Auxacolour with Cornmeal Agar. One laboratory stated they only speciate non-gynaecological isolates if specifically requested by a consultant. They use either VITEK or by germ tube (which only differentiates between *C. albicans* and non-*albicans* species). Similar to one laboratory in Northern Ireland, a laboratory in England stated they would use API 32C depending on the VITEK result but would also send samples to a reference laboratory, if necessary. Two laboratories stated they identify species using API 20C AUX.

3.2.6 Antifungal sensitivity testing

In Northern Ireland, two labs use VITEK for sensitivity testing with the media and incubation period varying according to the system specification. An additional two labs reported using a second method in addition to the VITEK system - sensititre and Etest on RPMI medium if extra sensitivities beyond fluconazole, voriconazole, AmpB and 5flucytosine were required. The final laboratory has no facility for local sensitivity testing and sends all isolates to a reference lab (either Leeds or Bristol). The anti-fungals used for routine testing are shown in Table 6. All labs test for AmpB and fluconazole sensitivity, with four of the laboratories also testing for 5Flucytosine. Testing for the other antifungals varies by laboratory. No additional antifungals are

tested on specific species. However, extra sensitivity testing is occasionally performed depending on the patient treatment.

Table 6 Antifungals routinely tested by the labs in NI as reported in 2012.

Laboratory	1	2	3	4	5
AmpB	✓	✓	✓	✓	✓
Anidulafungin				✓	
Caspofungin	✓		✓		✓
Fluconazole	✓	✓	✓	✓	✓
5Flucytosine	✓	✓		✓	✓
Ketoconazole					✓
Itraconazole			✓		✓
Posaconazole					✓
Voriconazole	✓			✓	✓

Similarly in England, two laboratories use VITEK for sensitivity testing and send some isolates to a reference laboratory for confirmation of identification and sensitivity. One laboratory stated it only performs sensitivity testing on blood culture isolates/sterile sites and non-gynaecological samples. Four laboratories reported using the ETest. The final laboratory stated they used VITEK but suggested that the test was not very good nor approved locally; *C. glabrata* and other non-*albicans* species were sent to a reference laboratory. This laboratory also stated that for non-*albicans* species they would also test the sensitivity to voriconazole as well as the three core antifungals. Depending on the type of infection (e.g. pancreatitis, endocarditis, or CNS infection), they would also test for 5Flucytosine. Routinely tested antifungals for each laboratory are displayed in Table 7.

Table 7 Antifungals routinely tested by the labs in England as reported in 2012.

Laboratory	E1	E2	E3	E4	E5	E6	E7
AmpB	✓		✓	✓	✓	✓	✓
Anidulafungin			✓			✓	
Caspofungin	✓			✓	✓		
Fluconazole	✓		✓	✓	✓	✓	✓
5Flucytosine	✓		✓			✓	
Ketoconazole							
Itraconazole			✓			✓	✓
Posaconazole							
Voriconazole	✓		✓	✓	✓	✓	✓

*Laboratory 2 does not routinely perform sensitivity testing, only on blood culture isolates/sterile sites.

3.2.7 Candida reporting

All responding labs in NI (N=5) and England (N=7) report all candidaemias to the relevant clinical team. All laboratories in NI report to the Public Health Agency whilst five out of the seven participating laboratories in England report to PHE (formerly HPA).

3.3 Case Review

3.3.1 Demographics

Out of 98 patients who had candidaemia in 2011 (N=83), 83 charts (85%) were available for review. The remaining 15 charts were distributed across a number of hospitals. The modal age group was those aged 75 years and older (25 individuals, 30.1%), followed by those aged 65-74 (23 individuals; 27.7%, Table 8). There were 48 individuals over 65 years compared to 35 individuals under the age of 65. Of the 83 individuals, 49 were male (59.0%) and 34 female (41.0%; Table 8). 82 individuals (98.8%) patients were resident in Northern Ireland.

Most patients (57 individuals, 68.7%) had a healthcare contact in the hospital setting, either as a day attendance or as part of an inpatient stay, within 6 months prior to the admission when they had a candidaemia. Chi square analysis indicated that in these patients recent attendance in a hospital setting was not linked to age ($p=0.23$). Over two thirds of those with candidaemia were admitted from their own home (58 individuals, 69.9%; Table 8), with almost 20% being transferred from another hospital. Just over 10% of individuals (9 persons) were admitted from a nursing home. Ward specialties were grouped into eight categories with 28 individuals (33.7%) being admitted directly to a general medical ward (Table 8) and 13 patients being admitted directly to ICU (15.7%) Whilst 44 individuals (53% of all patients) were been admitted to ICU for a period during their inpatient stay.

The largest proportion of patients were identified in the Belfast HSC Trust (41 patients, 49.4%), followed by the Northern HSC Trust (15 patients, 18.1%), South Eastern HSC Trust (11 patients, 13.3%), Southern HSC Trust (10 patients, 12%) and Western HSC Trust (6 patients, 7.2%), see Table 8.

Not taking into account those who died, the median length of stay (from admission to discharge) was 30.5 days (range 15 – 57.8 days; Table 8). All-cause mortality at the time of the case note review indicated that 42 individuals with candidaemia had died (50.6%; Table 8).This reflects the individual's outcome during the current admission or following their discharge for end of life care. 30 day mortality data, from the date of the positive specimen, was calculated at 35.1% (data only available for 57 patients).

Table 8 Patient characteristics for individuals with candidaemia in Northern Ireland during 2011.

Characteristic	Number (N=83)	Percentage of all candidaemia patients (95% CI)
Age Group		
Neonates	3	3.6 (1.2-10.1)
1-18	2	2.4 (0.7-8.4)
18-24	0	0.0 (0.0-4.4)
25-34	4	4.8 (1.9-11.7)
35-44	6	7.2 (3.4-14.9)
45-54	11	13.3 (7.6-22.2)
55-64	9	10.8 (5.8-19.3)
65-74	23	27.7 (19.2-38.2)
75+	25	30.1 (21.3-40.7)
Gender		
Male	49	59.0 (48.3-69.0)
Female	34	41.0 (31.0-51.7)
Country of Residence		
Northern Ireland	82	98.8 (93.5-99.8)
ROI	1	1.2 (0.2-6.5)
Recent hospital attendance (previous 6 months)		
Yes	57	68.7 (58.1-77.6)
No	26	31.3 (22.4-41.9)
Place admitted from		
Own Home	58	69.9 (59.3-78.7)
Nursing Home	9	10.8 (5.8-19.3)
Residential Facility	0	0.0 (0.0-4.4)
Transfer (other hospital)	16	19.3 (12.2-29.0)
Specialty admitted to		
Haematology	4	4.8 (1.9-11.7)
Surgical	20	24.1(16.2-34.3)
Medical	28	33.7 (24.5-44.4)
Renal	2	2.4 (0.7-8.4)
Oncology	2	2.4 (0.7-8.4)
Neonatal	2	2.4 (0.7-8.4)
ICU	13	15.7 (9.4-25.0)
Other*	12	14.5 (8.5-23.6)
Trust		
Belfast	41	49.4
Northern	15	18.1
Southern	10	12.0
South Eastern	11	13.3
Western	6	7.2
Patient deceased		
Yes	42	50.6 (40.1-61.1)
No	41	49.4 (38.9-59.9)
Median Length of Stay (days)	30.5	
Range (min, max)	2, 335	
25^{th}, 75^{th} percentile	15.0 – 57.8	

*Others included Cardiology, Neonatal ICU, Gynaecology, Urology, Nephrology, CF Unit, Respiratory and Gastroenterology.

3.3.2 Source

The source of candidaemia in the majority of patients was from intravascular line sepsis (24 patients, 29%; Table 9) or from an intrabdominal source (24 patients; 29%). There was no clear source of *Candida* infection for 14 patients (16.9%) and 12 patients (14.5%) who were immunosuppressed or were being treated with broad spectrum antibacterials.

Colonisation was reported in 35 out of 83 individuals. 12 individuals had a respiratory tract colonisation (14.5%), 9 urinary tract (10.8%), 7 skin (8.4%) and 7 other sites of colonisation (8.4%). However, the microbiology data contained in clinical notes may not have been complete, particularly for deceased patients. In these patients it was not appropriate to state that there was "no colonisation" and as such this may be under-reported. Colonisation is not reportable to the PHA and so it was not possible to validate these results.

Table 9 Site of candida infection based on an interpretation of the patient notes.

Site of Infection	Number (N=83)	Percentage of all candidaemia patients (95% CI)
Line sepsis	24	28.9 (20.3-39.4)
Abdominal	24	28.9 (20.3-39.4)
Urinary Catheter-associated	8	9.6 (5.0-17.9)
Endocarditis	3	3.6 (1.2-10.1)
Respiratory	3	3.6 (1.2-10.1)
Unclear/unknown	14	16.9 (10.3-26.3)
Other*	7	8.4 (4.1-16.4)

*Other sources included preterm neonates, neutropenic sepsis post-chemotherapy, mycotic aneurysm, secondary to hip replacement.

3.3.3 Diagnostics

The majority of patients did not undergo fundoscopy during their stay (70 individuals, 84%; Table 10). Of those who did, 90% (9 out of 10 receiving fundoscopy) had no evidence of ocular fungal infection. The median length of time between the date of candida isolation and date of fundoscopy was 3.5 days. No fundoscopies had been carried out prior to candidaemia diagnosis.

Of the 83 patients, 29 patients had echocardiography during their admission. However, only 15 (18.1%) of the 83 had an echocardiograph after a positive result

for *Candida*. 3 (20%) were seen to have vegetations requiring further investigation. The median length of time between the date of candida isolation and date of echocardiograph was 4 days. Most tests occurred between 2 and 13 days, although the range was from the day of diagnosis (day 0) to 84 days afterwards (Table 10).

Table 10 Other diagnostic tests on patients with candidaemia.

Test	Number	Percentage of patients (95% CI)
Patient had Fundoscopy (N=83)		
Yes	10	12.0 (6.7-20.8)
No	70	84.3 (70.5-90.6)
Unknown/unclear	3	3.6 (1.2-10.1)
Results (n=10)		
Evidence fungal infection	1	10.0
No evidence fungal infection	9	90.0
Timing (Time between fundoscopy and treatment start date (days))		
Median	3.5	
Range (min, max)	0, 10	
25^{th}, 75^{th} percentile	1.0, 6.5	
Patient had Echocardiography after positive result for *Candida* (N=83)		
Yes	15	18.1 (11.3-27.7)
No	64	77.1 (67.0-84.8)
Unknown/Unclear	4	4.8 (1.9-11.7)
Results (n=15)		
Vegetations	3	20.0 (7.0-45.2)
No vegetations	11	73.3 (48.0-89.1)
Unclear/unknown	1	6.7 (1.2-29.8)
Timing (Time between echo and treatment start date (days))		
Median	4	
Range (min, max)	0, 84	
25^{th}, 75^{th} percentile	1.75, 12.5	

3.3.4 ICU

Whilst 13 patients (13/83=15.7%) were admitted directly to ICU, 44 individuals (44/83= 53%) had had an admission to ICU within three months prior to candidaemia onset (Table 11). The median number of days spent in ICU was 8.5 (range 1-231). Of those admitted, 86.4% were mechanically ventilated, mostly for 3-14 days.

Table 11 Characteristics of patients who had an admission to ICU during their stay

ICU Characteristic	Number	Percentage of all candidaemia patients (95% CI)
Patients with any ICU admission during their hospital stay (N=83)		
Yes	44	53.0
Number of days in ICU		
Median	8.5	
Range (min, max)	1, 231	
25^{th}, 75^{th} percentile	4.0, 17.8	
Mechanical Ventilation (n=44)		
Yes	38	86.4 (73.3-93.6)
No	6	13.6 (6.4-26.7)
Duration of ventilation (n=38)		
<3 days	9	25.6 (14.6-41.1)
3-14 days	18	46.2 (31.6-61.4)
>14 days	11	28.2 (16.5-43.8)

3.3.5 Indwelling Lines and Drains

Of the 83 patients, 55 (66.3%) had a central venous catheter (CVC) in situ at some time prior to their candidaemia (Table 12). As removal was frequently not recorded, it was often difficult to calculate their time in situ. For those patients where dates were available (43 patients), the median length of time a patient had a CVC (including changes) was 13 days (range 1-1461). It was noted however that one patient had had a 'Portacath' inserted 4 years previously, totalling 1461 days. Most patients (80%) had only one line in at any one time, with a combined proportion of 11% having more than one line.

The median time between first line insertion and specimen date was 9.5 days. The median time between candida isolation and CVC removal was 1 day. However, for 9 individuals with two lines in situ, the median time for removal was 2 days. The median number of line changes (in the 30 days prior to candidaemia and the period following the ward being informed of the positive result) was 2.

Table 12 Indwelling lines and drain characteristics

Indwelling Lines and Drains	Number (n=83)	Percentage patients (95% CI)
CVC		
Yes	55	66.3 (55.6-75.5)
No	26	31.3 (22.4-41.9)
Unknown/unclear	2	2.4 (0.7-8.4)
CVC time (days) (n=43)		
Median	13.0	
Range (min, max)	1, 1461	
25^{th}, 75^{th} percentile	7.25, 23.7	
Number of lines in at any one time (n=55)		
1	44	80.0 (67.6-88.4)
2	9	16.4 (8.9-28.3)
3	2	3.6 (1.0-12.3)
Time between line insertion and specimen date		
Median	9.5	
Range (min, max)	0, 126	
25^{th}, 75^{th} percentile	2, 16	
Time between treatment start date and CVC removal (days) (n=43)		
Median	1.0	
Range (min, max)	0, 14	
25^{th}, 75^{th} percentile	0.0, 4.0	
Median time (days) for removal of CVC by number of lines (n=43)		
1 line	1	
2 lines	2	
3 lines	0	
No of line changes (n=55)		
Median	2	
Range (min, max)	1, 5	
25^{th}, 75^{th} percentile	1, 3	
Line removed after positive culture (n=55)		
Yes	21	
No	22	
Unknown/unclear	12	
Chest Drains (N=83)		
Yes	4	4.8 (1.9-11.7)
No	75	90.4 (82.1-95.0)
Unknown/Unclear	4	4.8 (1.9-11.7)
Duration in situ (n=4)		
<3 days	0	0.0 (0.0-49.0)
3-10 days	3	75.0 (30.1-95.4)
>10 days	1	25.0 (4.6-69.9)

3.3.6 Clinical Characteristics

Overall, 78 of the 83 (94%) patients had one or more risk factors. This meant that 5 individuals had none of the risk factors identified. However, three of these patients died during their hospital admission, with their primary reason for admission being for abdominal pain and a large AAA repair. Two patients had been admitted for burns and cholecystitis and were alive at discharge. The most common characteristic (aside from the 'other' category) was the use of total parenteral nutrition (TPN) (26 patients, 31.3%), followed by significant steroid use within the preceding 3 months (24 patients, 28.9%) (Table13). While it was recognised that having HIV, being an injecting drug user and having a transplant were important risk factors for candidaemia, none of the patients during 2011 presented with these factors. Approximately one third of patients (25 patients, 30%) (Table 13) had undergone surgery within 2 months prior to their candidaemia episode, with a further 16% of patients having a 'significant procedure' (for example, insertion/removal of stents, nephrostomy tubes and interventional radiography).

Table 13 Risk factors as recorded in the notes

Underlying clinical characteristics/Risk Factors	Number of patients(n=788)	Proportion of all candidaemia patients (%) (95% CI)
Diabetes	16	19.3 (12.2-29.9)
Chronic liver disease	5	6.0 (2.6-13.3)
Renal failure requiring intervention	12	14.5 (8.5-23.6)
Cardiac disease with symptomatic heart failure	13	15.7 (9.4-25.0)
Prematurity (neonates)	3	3.6 (1.2-10.1)
Neutropenia (polymorphonuclear neutrophils ≤500/mm^3) within previous month	9	10.8 (5.8-19.3)
Active neoplastic disease	23	27.7 (19.2-38.2)
COPD	12	14.5 (8.5-23.6)
Significant steroid use in previous 3 months (<20mg for 7 days)	24	28.9 (20.3-39.4)
Other immunosuppressants within 3 months	14	16.9 (10.3-26.3)
Total parenteral nutrition	26	31.3 (22.4-41.9)
Upper GI peritonitis due to GI perforation	8	9.6 (5.0-17.9)
Severe pancreatitis	3	3.6 (1.2-10.1)
Other**	46	55.4 (44.7-65.6)
Had Surgery (2 months prior to candidaemia)	25	30.1 (21.3-40.7)
Had Significant Procedure (2 months prior to candidaemia)	14	16.9 (10.3-26.3)
None	44	53.0 (42.4-63.4)

*Note patients may have had more than one risk factor present
**'Other' included alcohol abuse, Alzheimer's, other GI problems, fistulas and history of cancer

The median time between the onset of candidaemia and their discharge date was 21 days (range -12-256; Table 14). Onset of candidaemia was taken as when the patient began their treatment for infection. When no treatment start date was recorded, the specimen date plus 48 hours was used. If the number is negative, the patient was discharged or they died before the specimen was reported. The median time between beginning treatment and death was 8.6 days (for those patients who died in hospital), and 56.4 (for all the patients who died). The median time between the date of admission and the onset of candidaemia was 16.4 days.

Table 14 Timings of admission, discharge and death

Factor	Number
Median time between treatment start and:	
Discharge date (if alive)(days)	
Median	21
Range	-12, 256
25th, 75th percentile	12, 60
Death date (Patient died in hospital) (days)	
Median	8.6
Range	-2, 49
25th, 75th percentile	-1, 11
Death date (total patients) (days)	
Median	56.4
Range	-2, 388
25th, 75th percentile	0.8, 73
Median time between admission date and onset of candidaemia (days)	
Median	16.4
Range	
25th, 75th percentile	6.7, 19.1

3.3.7 Therapy

Antibacterial treatment

Antibacterials were prescribed to 81 of the patients (97.6%) in the 30 days prior to their candidaemia diagnosis (Table 15). Most patients received 3 (18 patients, 21.7%) or 4 (19 patients, 22.9%) antibacterials during this period, with 4 (4.8%) patients prescribed more than 7 antibacterials. An analysis of the antibacterials, received per person, indicated that the majority of patients were on a piperacillin/tazobactam combination (60 patients, 75%), closely followed by gentamicin (35 patients, 44%). Other common antibacterials were meropenem (30 patients, 37.5%), teicoplanin (26 patients, 32.5%), co-amoxiclav (22 patients, 27.5%) and metronidazole (21 patients, 26.3%; Table 16).

Table 15 Number of antibacterials prescribed per patient 30 days prior to candidaemia

Number of Antibacterials	Number of patients (N=83)	Proportion of patients (%) (95%CI)
0	2	2.4 (0.7-8.7)
1	12	14.5 (8.8-24.4)
2	10	12.0 (6.9-21.5)
3	18	21.7 (14.7-32.8)
4	19	22.9 (15.8-34.1)
5	7	8.4 (4.3-17.0)
6	11	13.3 (7.9-23.0)
7 or more	4	4.8 (2.0-12.2)

Analysis of antibiotic prescriptions

In total, 298 antibacterials were given to 80 patients with candidaemia in 2011 (Table 16). The most commonly prescribed were a combination of Piperacillin/Tazobactam (60 prescriptions, 20%), followed by Gentamicin (35 prescriptions,11.7%) and meropenem (32 prescriptions, 10.7%) (Table 16).

Table 16 Number of patients per prescribed antibacterial, and the total number of antibacterials issued, 30 days prior to candidaemia

Antibacterials (Grouped)	Number of patients (n=81)	Proportion of all patients (%)	Number of prescriptions (N=298)	Proportion of all prescriptions (%)
Aminoglycosides				
Amikacin	2	2.5	2	0.7
Gentamicin	35	43.8	35	11.7
Aztreonam				
Aztreonam	2	2.5	2	0.7
Third Generation Cephalosporins				
Cefotaxime	2	2.5	2	0.7
Ceftriaxone	5	6.3	5	1.7
Penicillins (extended spectrum)				
Amoxicillin	13	16.3	13	4.4
Combinations of Penicillins				
Piperacillin/Tazobactam	60	75.0	60	20.0
Co-Amoxiclav (Augmentin)	22	27.5	24	8.1
Beta-lactamase sensitive penicillins				
Benzylpenicillin	4	5.0	4	1.3
Beta-lactamase resistant penicillins				
Flucloxacillin	5	6.3	7	2.3
Carbapenems				
Ertapenem	1	1.3	1	0.3
Meropenem	30	37.5	32	10.7
Fluoroquinolones				
Ciprofloxacin	6	7.5	7	2.3
Levofloxacin	1	1.3	1	0.3
Glycopeptides				
Teicoplanin	26	32.5	26	8.7
Vancomycin	18	22.5	18	6.0
Macrolides				
Clarithromycin	12	15.0	12	4.0
Azithromycin	1	1.3	1	0.3
Tetracyclines				
Doxycycline	2	2.5	2	0.7
Tigecycline	2	2.5	2	0.7
Polymyxin				
Colistin	1	1.3	1	0.3
Combinations of sulfonamides				
Co-Trimoxazole (Septrin)	5	6.3	5	1.6
Imidazole derivatives				
Metronidazole	21	26.3	21	7.0
Nitrofuran derivatives				
Nitrofurantoin	1	1.3	1	0.3
Rifamycins				
Rifampicin	2	2.5	2	0.7
Lincosamides				
Clindamycin	1	1.3	1	0.3
Others				
Daptomycin	1	1.3	1	0.3
Linezolid	7	8.8	7	2.3
Trimethoprim	3	3.8	3	1.0

The most frequently prescribed antifungal, post candidaemia diagnosis, was fluconazole (44 individuals, 53%) followed by anidulafungin (20 individuals, 24.1%; Table 17).

Table 17 Number of patients prescribed antifungals following candidaemia diagnosis

Antifungals	Number of patients (N=66)	Percentage of all patients
Fluconazole	44	53
Caspofungin	10	12
Anidulafungin	20	24.1
Ambisome	12	14.5
Micafungin	9	10.8

***note patients may have been prescribed more than one type of antifungal**

Most patients (46.9%) were prescribed one antifungal (Table 18). However, 24.1% of patients (20 patients) were prescribed two, presumably due to cultures being speciated and therefore warranting a change in antifungal prescription.

Table 18 Number of antifungals prescribed per patient following a positive Candida result

Number of Antifungals	Number of patients (n=95)	Percentage of patients
0	19	22.9 (15.2-33.0)
1	39	46.9 (36.6-57.6)
2	20	24.1 (16.2-34.3)
3	4	4.8 (1.9-11.7)
4	1	1.2 (0.2-6.5)
5 or more	0	0.0 (0.0-4.4)

Prior to patients receiving a positive result for *Candida*, fluconazole was the most commonly prescribed antifungal (Table 19). Out of 17 prescriptions for fluconazole, 8 were given prophylactically and 9 were given empirically. The next most commonly prescribed antifungal was caspofungin (6 prescriptions) and anidulafungin (2 prescriptions), both empirically. All other antifungals were prescribed for empirical reasons.

No patients were recorded to be on voriconazole following a positive result. It was noted that 11.1% of neutropenic patients were prescribed ambisome as per guidelines – others were prescribed voriconazole, anidulafungin, fluconazole or nothing.

Table 19 Total number of antifungals issued, preceding and following a positive candidaemia result, during 2011.

Antifungal	Number of prescriptions
Preceding positive result	
Fluconazole	17
Caspofungin	6
Anidulafungin	2
Ambisome	1
Micafungin	1
After positive result	
Fluconazole	50
Anidulafungin	21
Ambisome	12
Caspofungin	10
Micafungin	9
AmpB	1

*note not representative of patient numbers, table displayed per antifungal rather than patient

Comparisons with the Point Prevalence Survey (PPS) of Hospital-acquired Infections and Antimicrobial Use 2012[11]

The overall prevalence of antimicrobial use in acute care hospitals in NI, during 2012, was 29.5% with the greatest use in ICU (55.6%). In this audit, 97.6% (81/83) of patients were prescribed an antibacterial in the 30 days prior to their candidaemia diagnosis. The higher prescribing of piperacillin/tazobactam in candidaemia patients reflects the findings of the PPS, where piperacillin/tazobactam was the most prescribed antimicrobial at the time of the survey (20.4%).

4.0 Discussion

4.1 Summary

This audit has confirmed that the numbers of candidaemia reported through voluntary laboratory reporting in NI are accurate; reflected in the similarity between voluntarily reported and validated data. Similar diagnostic methods were identified in NI and England. Whilst known risk factors were prevalent in the NI candidaemic population there were 5 cases who had no known risk factors. Without a comparison group it is not possible to infer if the case mix of the NI population increases the risk of candidaemia infection.

4.2 Interpretation of findings

The main aim of this audit was to determine why candidaemia rates were almost twice as high in NI, when compared to England and Wales. Whilst this audit was unable to identify specific reasons behind the higher rates of candidaemia locally, it is known from previous studies that variations in clinical practice, an increased awareness of hospital staff and the use of medical interventions are all likely to contribute to regional and unit variation.[17,18] Therefore, for this audit a number of hypotheses were generated. For example, the variation may relate to differences in laboratory diagnostic methods (ascertainment bias) or variations in reporting (reporting bias). It was also suggested that the differences may be due to differences in case mix in the NI population resulting in a profile of higher risk patients. As a secondary aim, some aspects of the management of candidaemia infections were audited. This was determined as relevant in view of the higher rate locally and the need to ensure accepted guidelines were adhered to.

As expected, the validation exercise showed that the completeness of reporting of Candidaemia isolates was high, with 95.6% of all diagnosed candidaemia isolates being reported to the PHA over the last decade. Thus, reporting bias remains a possible hypothesis for higher rates in NI. This is conceivable as the data for *S.aureus* voluntary reporting in England shows 15-20% underreporting compared to the mandatory scheme. Similar higher rates are also observed for other bacteraemias, including Proteus[1] spp. and glycopeptide resistant enterococci[2], where rates in NI are consistently higher than England and Wales. Given the difference in the size of the population, between England and NI, and the number of diagnostic laboratories it is feasible to suggest that reporting is more complete locally but a formal validation study would be needed to confirm this.

[1] http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317138737263
[2] http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136652736

Over the ten year period approximately 94% of all candidaemia isolates were speciated. The speciation of isolates is used to inform appropriate antifungal treatment.[11] Although this study assessed candidaemia speciation prior to the issue of the BSMM guidelines, there did not appear to be any systematic difference in the proportion speciated pre or post guidelines. This high proportion is reassuring as it indicates that the information is available to guide antifungal choice.

Laboratory diagnostic methods throughout NI and England were broadly similar. All laboratories surveyed used one of two commercial blood culture systems, followed by subculture in conditions that would support the growth of *Candida* species. In NI, generally the number of candidaemias, as a proportion of the total number of blood cultures, increased with the size of the Trust. A second denominator, average occupied bed days, was used to examine the average number of days per blood culture across the laboratories in NI and in England. In NI, there was over a twofold variation in the average number of days per blood culture between the laboratory that tested most frequently and the one that tested least frequently. This must be interpreted with caution as it may reflect differences in the case mix between the laboratory populations. Comparative data for England showed that on average laboratories there test similar frequencies to the most frequent testing laboratory in NI. However, in England there was also great variation in testing ranging from 5.9 days per blood culture to 47.8 days per blood culture. This variation could be explained by the wide variety of specialist hospitals available in England. It should be noted that this observation was based on data over a 1 year period.

Risk factors for candidaemia are well established[12], especially in the critically ill.[19] The case review revealed that known risk factors were prevalent in the NI candidaemic population with 94% having one or more risk factors. For example, many patients had received antibacterials in the previous 30 days (98%), were colonised (42%), used steroids (29%), had surgery in the 30 days prior to the positive specimen (30%), had TPN (31%), central venous catheter insertion (66%) and diabetes (19%). What was interesting was that 5 patients did not have any of these risk factors. Three of these patients died during their hospital admission, with their primary reason for admission being for abdominal pain and a large abdominal aortic aneurysm repair.

A secondary aim of this audit was to examine the management of Candidaemia infections. The British Society for Antimicrobial Chemotherapy (BSAC) guidelines for the investigation and treatment of endocarditis recommend echocardiography for all patients with candidaemia within the first week of isolating the organism or within the first 24 hours if the suspicion of infective endocarditis is high.[20] This is one of the few recommendations for routine echocardiography in the light of the high morbidity of endocarditis with candida species and the frequency of endocarditis in candidaemic patients.[20] Of the patients assessed as part of this audit, only 18% had an echocardiography carried out within the recommended time after their candidaemia diagnosis. Similarly, fundoscopy has been recommended as a gold standard test for organ involvement in the most recent European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the diagnosis and management of *Candida* diseases.[21] Although these guidelines were published a year after the case review took place, only 12% of patients received a fundoscopy following their diagnosis. A similar low uptake of fundoscopic examination was observed in a population of candidaemic patients in England and Wales.[18] It is not possible to ascertain what proportion of this low uptake relates to poor note keeping which was evident during the audit. Further work to ascertain whether this does reflect poor documentation should be pursued. However, it is unlikely that poor notes alone accounts for the 88% that did not receive this procedure.

Another recommendation by the BSMM[11] is the removal of any CVC within 48 hours of identification of candidaemia. This study identified that 55 of the 83 patients had a CVC in situ at some time prior to their candidaemia. However, it was often not recorded when CVCs were removed making it difficult to calculate their time in situ. For those patients where dates were available (43/55 patients) the median time between candida isolation and CVC removal was 1 day. Whilst the evidence is inconclusive about whether or not CVC removal had an impact on mortality[18] it is important that dates pertaining to their insertion and removal are accurately recorded.

4.3 Limitations

The validation exercise confirmed the high level of reporting in NI laboratories but it was not possible to ascertain if there is an element of reporting bias in England. A major limitation for examining why rates are higher in NI is the lack of comparative data for the validation study and the clinical case review. This study was retrospective by design with a reliance on patient notes for all aspects of the clinical case review. The use of one

individual as the main reviewer of the case notes is a strength as this ensured consistency with how the notes were interpreted. However, clinical notes may be incomplete. Finally, this audit has identified some important learning about the management of candidaemia which is particularly relevant in light of the higher rates locally.

4.4 Conclusion

This audit confirmed that the observed rates of candidaemia in Northern Ireland are accurate. Most candidaemia patients had one or more of the known risk factors for infection, as expected. Given the high rates of candidaemia in Northern Ireland, a focus on the appropriate management of candidaemia infections is required. This includes improved awareness of clinical guidelines, improved accuracy of clinical notes, the use of diagnostic tests to identify complications following candidaemia diagnosis, timely CVC removal and appropriate antifungal treatment.

4.5 Future Work

The following areas have been suggested for future work:

1. Raising the awareness of existing[11,12] and more recent guidelines[21, 24] for improving the management of Candidaemia infections.
2. Improving the recording of patient notes which is essential to inform the appropriate management of the infection. Having this information readily available is particularly relevant for identifying patient groups who may benefit from prophylaxis which is known to improve morbidity and mortality outcomes [21]. In particular, it was noted that it was difficult to find information about Candidaemia, recording of microbiology was poor and seemed to be misinterpreted on several occasions, there was no clear order to some of the notes, there were problems with identifying drugs prescribed in ICU, there was no record of CVC insertion / removal and no APACHE II score in ICU patients. Some ICUs used a daily review proforma which lists current antimicrobials and duration of treatment/current lines in situ and duration of line or has a specific page for microbiology results, these were easier to use for audit purposes. One suggestion is to amend these for general use and share across the Trusts.
3. All laboratories in Northern Ireland gave advice about how and when to take blood cultures. Further work could include an audit on implementation of these policies.
4. Bloodstream infections associated with CVC insertion are a major cause of morbidity. The 2012 Prevalence Survey of Hospital Acquired Infections and Antimicrobial Use[22] showed the presence of a CVC was associated with higher HAI prevalence (20.5%, $p<0.01$). While this audit did not specifically assess CVC care, attention should be given to raising the awareness and adherence to the CVC Care Bundle.[23] Particular attention should be given to the recording of information for CVC removal (including date, location, and signature and name of operator undertaking removal).

5.0 Review of standards

S1 All invasive *Candida* to be reported to the PHA[13]

Exceptions: None

Compliance: 1027/1074 (95.6%)

Non-compliance: 47/1074 (4.4%)

Health Protection Agency (HPA) guidelines published in 2012 state that all invasive *Candida* should be reported to HPA. In total by using a validation exercise 1027 out of 1074 (95.6%) isolates were identified to the Public Health Agency (PHA) through the voluntary reporting scheme. 47 (4.4%) were not reported to the PHA. For voluntary reporting this standard is high.

S2 All fungi obtained from sterile sites should be identified to species level[11]

Exceptions: None

Compliance: 982/1027 (95.6%)

Non-compliance: 45/1027 (4.4%)

The British Society for Medical Mycology provided microbiology standards of care in that all fungi obtained from sterile sites, including blood and continuous ambulatory peritoneal dialysis fluids (CAPD), and intravenous line tips should be identified to species level. In total, 982 results out of 1027 were identified to species level (95.6%).

S3 All patients with candidaemia should have central venous catheters (CVC) removed or replaced within maximum 48 hours of *Candida* spp. being identified in a blood culture[11]

Exceptions: None

Compliance: See below

Non-compliance: See below

There was some difficulty identifying when central lines were removed from patients as this was generally not well recorded in the notes (including the nursing notes). A removal date was available for 41 of 55 (74.5%) patients who had a CVC in situ. 21 patients (38.2%) had their CVC removed immediately after a positive culture as stated in the notes. However, the median time between *Candida* identification and CVC removal was 1 day. For patients who had two lines present at any one time, the median time for removal was 2 days. This fits the current standard of lines being removed within 48 hours of culture.

S4 All patients should be treated with a systemic antifungal agent at an appropriate dose, and breakthrough fungaemia treated with an alternative agent[11]

Exceptions: None

Compliance: 64/83 patients (77.1%)

Non-compliance: 19/83 patients (22.9%)

64 out of 83 patients were prescribed an antifungal following a positive result for Candidaemia species. 20 (31.3%) of these patients received more than one type of antifungal, indicating treatment for a breakthrough candidaemia. This could be an indication that alternative agents were used when required. 19 patients (22.9%) did not receive any antifungals. Due to the nature of the data collection tool it was not possible to determine if the appropriate antifungal dose was given.

S5 Practice and procedures that improve the quality of blood culture investigations should be implemented[14]

Exceptions: None

Compliance:

Non-compliance:

All laboratories in Northern Ireland HSC Trusts gave advice about how to take blood cultures and in practice most are taken when patients have fevers and/or rigors or are non-specifically unwell. However, the Trusts are generally not following any rigid protocol as to when blood cultures should be taken.

6.0 Dissemination to date

Aspects of this audit were presented at:

- Queen's University Belfast Centre for Infection and Immunity Young Scientist Symposium, Belfast, on 22nd February 2013 (poster presentation)

- Hospital Infection Society (HIS) and Infection Prevention Society (IPS) Spring Meeting, Nottingham, on 24th April 2013 (poster presentation)

- 5 Nations Health Protection Conference, Dublin, on 14th May 2013 (poster presentation)

- Northern Ireland Regional Microbiology Audit Group, Belfast City Hospital, on 19th June 2013 (oral presentation)

- Irish Fungal Society (IFS) meeting, NUI Maynooth, on 20th June 2013 (oral presentation)

7.0 Learning Points from the Auditing Process

- The initial pilot demonstrated the clinical proforma was too long. At first it took 60-90 minutes to complete, especially looking for the APACHE II and stop/start date for antibacterial prescriptions. A second proforma, amended by the steering group, was much easier to complete.

- Some outputs should be planned prior to the data collection. The auditors should plan how the data will be presented in advance, while still allowing a degree of flexibility upon analysing the results.

- A second data collector was beneficial to reduce the time taken to complete the proforma and improve on data quality through correction/validation.

- It was useful to know the specimen date of the positive *Candida* result – often patients were admitted for the whole of 2011 and it took time looking through the notes for details of their candidaemia episode, particularly when microbiology reports were missing.

- Proformas should be printed on one side of the page to prevent confusion. Consideration should be given to the use of user-friendly tools for data capture and entry e.g. ‘scannable’ proformas, using web-based questionnaires.

8.0 Action Plan

	Action *(i.e. How Recommendation will be implemented)*	Date Implementation to be completed	Staff Responsible	Manager Responsible
1	Raise the awareness of existing and more recent guidelines for improving the management of Candidaemia infections by circulating ESCMID/BSMM and IDSA guidelines to Regional Microbiology Network/consultant microbiologists. (Refer to page 29 of the report)	30/04/14	RS	LP
2	Share the ICU daily review proformas to CCaNI with the suggestion to share across Trusts to improve the recording of patient notes, in particular: • recording of microbiology • identification of drugs prescribed in ICU • recording of CVC insertion/removal Report to also be presented to CaNNI.	30/04/14	RS/LP	LP
3	Share data on the proportion of isolates tested for antifungals and recommend to the Regional Microbiology Network that this is reviewed (refer to page 21 of the report)	30/04/14	TW	TW
4	Circulate DH CVC Care Bundle to Trust Medical Directors; highlight the recording of information for CVC removal (including date, location, and signature and name of operator undertaking removal) (Refer to page 31 of the report).	30/04/14	RS	LP
5	Present findings to the HCAI Strategic Steering Group at DHSSPS	31/01/14 (Meeting pending)	RS	LP

9.0 References

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Appendix 1

Laboratory questionnaire

Section 1 relates to current ward practice for the calendar year 2011. Section 2 refers to the same time period but ask questions about laboratory practices during this time.

Please complete the questionnaire and return by [Date]:

Section 1 Ward practice

1. Do you have clinical guidelines to determine when blood cultures for positive candidemia should be taken?

   ☐ Yes **If yes, please attach.**

   ☐ No

Section 2 Laboratory Practice

2.1 Blood culture methods

1. What blood culture method do you use?

   ☐ Bactec

   ☐ BacT Alert

   ☐ Other → Please list: _____

2. What blood culture medium do you routinely use?

   ☐ Standard Aerobic and Anaerobic Bactec bottles

   ☐ Standard BacT Alert aerobic and anaerobic

   ☐ Special fungal bottles → Indicate when: _____

3. Does Candida grown in your lab routinely use blood culture medium with no special procedures such as cap venting?

   ☐ Yes

   ☐ No **If no, please specify special procedures:** _____

4. Does investigation for Candida have to be requested by the clinician?

   ☐ Yes ☐ Other **If other, please specify:** _____

   ☐ No

1

5. What is the normal incubation period for Candida blood cultures?

   ☐ 5 days

   ☐ 6 days

   ☐ 7 days

   ☐ Fungal bottles 14 days

   ☐ ?SBE 21 days

   ☐ ?SBE 14 days

6. Is the blood culture bottle terminally sub-cultured?

   ☐ Yes

   ☐ No

2.2 Candida isolation procedures from positive bottle

1. What media is a positive bottle sub-cultured to?

   ☐ Blood Agar, Sabaraud, CAN-2 Chromogenic (BioMerieux)

   ☐ Blood Agar, Sabaraud

2. What incubation conditions are used for sub-cultures?

   ☐ 37°c / Air

   ☐ 35°c / Air

   ☐ 35°c / CO_2

3. What incubation period is used for sub-cultures?

   ☐ 24-48 hours

   ☐ Other → **If other, please specify:** _____

2

2.3 Candida Speciation

1. Do you routinely identify all Candida to species level?

☐ Yes

☐ No **If no, which ones are speciated:** _____

2. What identification procedure do you use?

☐ API 32C

☐ VITEK

☐ Other → **If other, please specify:** _____

2.4 Candida sensitivity testing [Blood Culture Isolates only]

1. Please specify the method used:

☐ Vitek

☐ Etest

☐ Sensititre

☐ Other → **If other, please specify:** _____

2. What antifungals do you routinely test on ALL Candida isolates?

☐ Fluconazole

☐ Voriconazole

☐ Ketoconazole

☐ Itraconazole

☐ Amphotericin

☐ Anidulafungin

☐ Campofumycin

☐ Caspofungin

☐ 5Flucytosine

☐ Posaconazole

5. What antifungals do you test on particular Candida species?

Species	Antifungal

2.5 Reporting

1. Do you report all Candida bloodculture isolates to the Ward?

☐ Yes

☐ No **If no, specify what is reported:** _____

2. Do you report all Candida bloodculture isolates to the PHA?

☐ Yes

☐ No **If no, specify what is reported:** _____

---------- **Ends** ----------

Appendix 2

Version 9.0 16/11/2012

Candidaemia proforma

Section 1 – Demographic/Patient Characteristics

1) Patient Information

Patient Identifier: ☐☐/☐ Age: 18-24 ☐ 25-34 ☐ 35-44 ☐ 45-54 ☐ 55-64 ☐ 64-74 ☐ 75+ ☐

Sex: M / F

Country of residence: _____

Admission date: ____/____/____ Hospital discharge date: ____/____/____

2) Specialty admitted to:

Haematology ☐ Surgical ☐ Medical ☐ Renal ☐

Oncology ☐ Neonatal ☐ ICU ☐ Other ☐ → **Please specify:** _____

3) Main Diagnosis

Primary reason for admission: _____

_____

Secondary reason (if applicable): _____

_____

4) Recent surgery

Surgery during the past 2 months prior to the candidaemia: ☐ Yes → **If yes list all below** ☐ No

Date: ____/____/____ Procedure: _____

Date: ____/____/____ Procedure: _____

Date: ____/____/____ Procedure: _____

5) Implantation

Date: ____/____/____ Procedure: _____

Date: ____/____/____ Procedure: _____

Section 2 – Patient Journey prior to Candidaemia episode

1) Place admitted from: Own Home ☐ Nursing Home ☐ Residential Facility ☐

Transfer from other hospital ☐ → **Hospital Name:** _____

2) Previous hospital interaction in the last 6 months? ☐ Yes → **If yes list all below** ☐ No

1

Version 9.0 16/11/2012

Hospital	Patient Type	Date of admission/visit	Date of discharge *if applicable*
	Inpatient ☐ Day Services ☐		
	Inpatient ☐ Day Services ☐		
	Inpatient ☐ Day Services ☐		
	Inpatient ☐ Day Services ☐		

Section 3 – Outcome following Candidaemia diagnosis

1) Mortality

Alive: ☐ Yes → **If yes, date confirmed:** ____/____/____ ☐ No

Dead: ☐ Yes → **If yes, date of death:** ____/____/____ ☐ No

2) Cause of death: _____

_____

Section 4 – Underlying clinical characteristics

1) Pre-existing co-morbidities (predispose patients to infection, alter defence mechanisms or cause functional impairment):

a) Diabetes ☐

b) Chronic liver disease ☐ → **Underlying cause:** _____

c) Renal failure requiring intervention ☐

d) Cardiac disease with symptomatic heart failure ☐

e) HIV ☐

f) Prematurity (neonates) ☐ → **Birth weight :** _____g **Gestation:** _____**weeks**

2

g) Neutropenia (polymorphonuclear neutrophils ≤500/mm^3) within previous month ☐

h) Injecting drug user ☐

I) Active neoplastic disease ☐

j) COPD ☐

k) Significant Steroid Use in previous 3 months (>20mg for 7 days) ☐

l) Other immunosuppressants within 3 months ☐

m) Total Parenteral Nutrition within last 30 days ☐

n) Upper GI peritonitis due to GI perforation ☐

o) Severe pancreatitis ☐

Other: _____

_____

_____

Section 5 – Indwelling lines and other drains

1) In the 30 days prior to positive specimen [use nursing notes]:

			Date inserted	Date removed
1) CVC	☐ Yes	→ **If yes**	1) ___/___/___	___/___/___
	☐ No		2) ___/___/___	___/___/___
	☐ Not available		3) ___/___/___	___/___/___
			Central lime removed after culture? ☐ yes ☐ no	
2) Chest drains	☐ Yes	→ **If yes**	☐ <3 days ☐ 3-10 days ☐ >10 days	
	☐ No			
	☐ Not available			

3) Abdominal Drains ☐ Yes ☐ No ☐ Not available

4) Other: _____

_____

Section 6 – ICU/HDU admission

1) ICU admission within 3 months prior to Candidaemia

ICU admission: ☐ Yes → **If yes**, number of ICU days _____ ☐ No

Mechanical Ventilation: ☐ Yes→ **If yes**: how long for? ☐ <3days ☐ 3-14 days ☐ >14 days ☐ No

Section 7 – Candidaemia diagnosis

1) Your assessment of the source of infection: _____

_____

_____

_____

2) Areas known to be colonised with Candida Spp (in previous 3 months)

Skin ☐

Respiratory tract ☐

Urinary tract ☐

Other ☐→ **Please specify**: _____

3) Diagnostics

a) Fundoscopy carried out ☐ Yes→ **If yes**: Date: ___/___/___ ☐ No

Result _____

b) Echocardiography carried out ☐ Yes→ **If yes**: Date: ___/___/___ ☐ No

Result _____

Section 8 – Antibiotic History

1) Prior antibiotic history (use during the 30 days, or relevant antibiotic therapy during current admission, prior to candidaemia episode) :

☐ Yes → **Please list**
☐ No

2) Please list Antibiotic and start/end dates prior to candidaemia

Drug Name / Class	Route (PO = oral / IV = intravenous)	Indication (E = Empirical / P = prophylactic / D = Definitive)

Section 9 – Antifungal History

1) Antifungal treatment during the 30 days preceding positive blood culture result:

Antifungal	Dose (X mg/ X days)	Route (PO = oral / IV = intravenous)	Indication (E = Empirical / P = prophylactic / D = definitive)	Date started (DD/MM/YYYY)	Date ended (DD/MM/YYYY)

2) Antifungal treatment after candidaemia established (definitive therapy):

Drug Name / Class	Route (PO = oral / IV = intravenous)	Date started (DD/MM/YYYY)	Date ended (DD/MM/YYYY)

Section 10 – Microbiology data

1) Candidaemia microbiology [taken from laboratory data]

Specimen date: ____/____/____ Lab Ref No: _____

Species:

C. albicans ☐ C. glabrata ☐

C. parapsilosis ☐ C. krusei ☐

C. tropicalis ☐ Other Candida species ☐ **Please specify:** _____

2) Antifungal Sensitivity profile:

Antifungal	Result
AmpB	R / S / I / not tested
Anidulafungin	R / S / I / not tested
Caspofungin	R / S / I / not tested
Fluconazole	R / S / I / not tested
5Flucytosine	R / S / I / not tested
Ketoconazole	R / S / I / not tested
Itraconazole	R / S / I / not tested
Posaconazole	R / S / I / not tested
Voriconazole	R / S / I / not tested
Micafungin	R / S / I / not tested

Appendix 3

Table 20 The number and age-specific* rates of candidaemia per 100,000 population in Northern Ireland, 2011.

	Female			Male		
Age Group	**Number**	**Population***	**Rate**	**Number**	**Population***	**Rate**
<1	0	12340	0	3	12910	23.24
1-4	0	48516	0	1	50616	1.98
5-9	0	54178	0	0	57109	0
10-14	0	58002	0	0	61032	0
15-44	9	378091	2.38	6	372209	1.61
45-64	11	223331	4.93	15	218809	6.86
65-74	11	76524	14.37	10	69076	14.48
75+	13	72558	17.92	18	45562	39.51

*Taken from Northern Ireland Census 2011, NISRA.

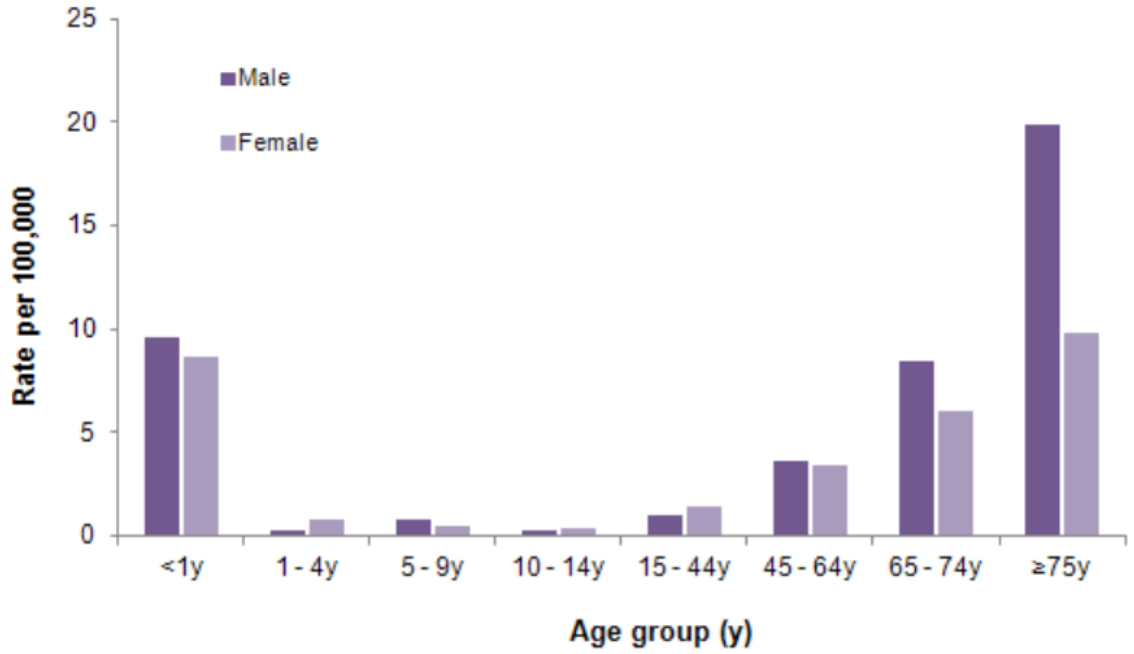

Figure 9 The number and age-specific* rates of candidaemia per 100,000 population in England, Wales and Northern Ireland, 2011 (taken from the HPA Health Protection weekly report[16]).

*Taken from Northern Ireland Census 2011, NISRA.

Appendix 4

Table 21 The number and proportion of *Candida* isolates as reported to the Public Health Agency, 2002-2010

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010
Number Unreported	1	2	8	4	10	7	5	2	6
Total Validated	80	76	96	91	119	123	132	97	117
Proportion un-reported (%)	1.25	2.63	8.33	4.40	8.40	5.69	3.79	2.06	5.13
Proportion reported (%)	98.75	97.37	91.67	95.60	91.60	94.31	96.21	97.94	94.87

Table 22 The number and proportion of *Candida* reports, identified to species level, as reported to the Public Health Agency

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number unspeciated	6	0	3	7	8	12	1	1	4	3
Proportion unspeciated	7.50	0	3.13	7.69	6.72	9.76	0.76	1.03	0.85	3.03

Table 23 The number and rate (per 1000 blood cultures) of candidaemias, by lab, 2009-2011

Laboratory	Number of Candidaemias	Total Blood Culture Requests*	Rate of Candidaemia (/1000)
1	48	21651	2.22
2	29	23679	1.22
3**	18	13955	1.29
4	42	28261	1.49
5	162	85439	1.90
TOTAL	299		

*As reported through the EARS-net questionnaire data collection

**Note 2010 blood culture request data missing, adjusted no. of candidaemias

Note: Merger of labs Tyrone County to Altnagelvin, Belfast City to Royal Victora and Causeway to Antrim Area in 09/10

Table 24 The number and rate (per 10,000 occupied bed days) of candidaemias, by lab, 2009-2011

Laboratory	Number of Candidaemias	Total Bed Days*	Rate of Candidaemia (/10,000)
1	48	694093	0.69
2	29	696823	0.42
3	18	738204	0.24
4	42	862237	0.49
5	162	1865173	0.74
TOTAL	299		

*As reported through DHSSPS(NI)

Table 25 The average number of bed days per blood culture taken, by lab, 2009-2011

Laboratory	Total Bed Days*	Total Blood Culture Requests*	Bed days / Blood Culture Request
1	694093	21651	32.06
2	696823	23679	29.43
3**	738204	13955	52.90
4	862237	28261	30.51
5	1865173	85439	21.83
Mean			*33.35*

**only two years of data

Appendix 5

Abbreviations

AAA	Abdominal aortic aneurysm
EARS-net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
C. difficile	*Clostridium difficile*
CVC	Central venous catheter
HCAI	Healthcare associated Infections
IFD	Invasive Fungal Disease
MRSA	Meticillin Resistant *Staphylococcus aureus*
PPS	Point Prevalence Survey
PHA	Public Health Agency
SBE	Sub-acute bacterial endocarditis
Spp.	Species (plural)
TPN	Total parenteral nutrition

Appendix 6

Project Steering Group

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