The Regulation and Quality Improvement Authority

Regional Audit of Cytomegalovirus (CMV) Colitis

A retrospective regional audit of Cytomegalovirus (CMV) laboratory diagnostics in Crohn's/Colitis patients in Northern Ireland

August 2018

www.rqia.org.uk

Assurance, Challenge and Improvement in Health and Social Care

Contents **Page**

Executive Summary

Background/Rationale

In 2011, a pilot study was undertaken to assess clarity and consistency in the identification of the virus cytomegalovirus (CMV) in inflammatory bowel disease (IBD) patients, particularly in those with severe acute colitis (SAC) or those with steroid refractory colitis (SRC). This study consisted of assessing and comparing not only the type of CMV laboratory investigations performed, but also the therapeutic management of the CMV and surgical intervention (colectomy rate) in a small cohort (n=30) of inflammatory bowel disease (IBD) patients. The data were presented at the Ulster Society of Gastroenterology (USG) meeting in the autumn of 2013[1].

Guidance at the time of this pilot study was unclear on the diagnostics required to identify CMV colitis, with no clear direction as to the type of specimen (typically blood, tissue or faecal samples) to submit for laboratory diagnosis and the subsequent clinical interpretation of the laboratory results[2]. This prompted further study in the form of this RQIA funded regional audit to identify the practices of laboratory investigation in IBD patients within the five Health and Social Care (HSC) Trusts and so bring about more effective patient focused test requesting and result interpretation.

Aim

The aim of this audit is to improve the detection and management of CMV colitis in patients with IBD and reduce the colectomy rate associated with this condition.

Objectives

The audit objectives are to:

- Review the current practices in tissue sample submission within the five HSC Trusts for the laboratory (virology and histopathology) investigation of CMV.

- Establish a baseline within the five HSC Trusts in relation to submission of samples of blood and or faeces for virology laboratory investigation of CMV.

- Review the current turn-around-times (TAT) for the virology laboratory investigation of CMV in IBD patients within the five HSC Trusts and establish a baseline for rapid reporting of CMV positive results by means of a phone call to the requestor.

- Review the current use of antivirals in CMV positive IBD patients within the five HSC Trusts.

- Establish a baseline of comparative case numbers for CMV positive SAC/SRC and non-acute IBD cases in terms of surgical intervention.

Summary of Key Findings

This regional audit was a cross-sectional study over a three year time-period, January 2010 - March 2013. A total of 277 IBD (Ulcerative Colitis (UC) and Crohn's Disease (CD) patients with evidence of CMV investigation formed the sample cohort. All 277 patients attended one of the five HSC Trusts as either an inpatient or an outpatient on these occasions. Of the 277 patients, a total of 106 were further grouped as 'severe acute colitis and/or steroid refractory colitis (SRC)'. Severe acute colitis is defined as a severe flare of colitis with more than 10 bowel motions per day, continuous abdominal pain and severe toxic symptoms; steroid refractory colitis is defined as a severe form of colitis lacking a meaningful clinical response to steroid treatment after 7 days (oral) or 10 days treatment (IV). A total of n=171 patients were defined as the non-acute IBD cohort.

Data were collected by IBD and endoscopy nursing staff and entered into an anonymised access database which included five tab fields of:

1. demographics
2. baseline clinical data
3. clinical course
4. clinical data investigation
5. virology laboratory results.

Once complete, the database was prepared for interrogation/query function to enable assessment against the audit standards.

Audits Standards and percentages achieved

The two patient cohorts were assessed against the audit standards:

- Standards 1A and 1B were applied to 106 patients (SAC/ SRC cohort).
- Standards 2, 3, 4 and 5 were applied to the full audit sample (N=277); both SAC/SRC (N=106) and Non acute colitis cohorts (N=171).

Standards 1A and 3 were used to measure compliance, whilst the remaining standards (1B, 2, 4 & 5) established a baseline in these areas.

Table 1: Audit Standards

No.	Standard	Target	Achieved
1A.	*During admission, all IBD patients presenting with severe acute colitis (SAC) or steroid-refractory colitis (SRC) to have a colonic biopsy (tissue) specimen submitted for histopathology (N=106).*	*100%*	Compliance 92%
1B.	*During admission, all IBD patients presenting with severe acute colitis (SAC) or steroid-refractory colitis (SRC) to have a colonic biopsy (tissue) specimen submitted to the Regional Virus Laboratory (RVL) for CMV DNA testing via Polymerase Chain Reaction (PCR). (N=106).*	*baseline*	Established baseline 70%
2.	*Establish a baseline for specimen submission of blood and or faeces to the Regional Virus laboratory (RVL) for CMV investigation, and the appropriate laboratory test requests in the SAC/SRC cohort (N=106).*	*baseline*	Established baseline for specimen receipt: 1. 27% CMV Blood for IgG screening test 2. 50% CMV Blood for IgM screening test 3. 51% CMV Blood for PCR *4.* 29% CMV Faeces for PCR

No.	Standard	Target	Achieved
3.	*Upon confirmation of CMV colitis via a combination of colonic tissue histology and/or tissue PCR, patients should be treated with antivirals (either Ganciclovir or Valganciclovir) for a total of 14-21 days if appropriate (N=277)*	*100%*	Compliance 37%
4.	Establish if a protocol for rapid communication (i.e. telephoned to requestor) of virology laboratory results is in place to enable timely initiation of antiviral therapy where possible (Positive CMV PCR results in the IBD cohort (N=34 of 277).	*baseline*	Established baseline: 50% (positive CMV PCR results telephoned to requestor)
5.	Establish a baseline of surgical intervention in the form of a colectomy in CMV positive IBD patients (N=211 of 277) (91 of 106 SAC/SRC, and 120 of 171 of the non-acute IBD cohort).	*baseline*	Established baseline: 1. 28%: Colectomy rate in SAC/SRC Cohort 2. 50%: Colectomy rate in CMV positive SAC/SRC cohort 3. 4%: Colectomy rate in non-acute IBD Cohort 4. 6%: Colectomy rate in CMV positive non-acute IBD patients

Full discussions in relation to these standards are available within the report's 'findings' section (P16).

Recommendations

This audit has primarily found a need to

- Better define test requesting protocols (optimal sample required (e.g. tissue and blood).
- Develop protocols for optimal test requests (IgG and PCR).
- Work towards timeliness in both test request and result reporting.

This audit has also identified a 'high risk patient group' (those severe acute colitis and/or SRC patients) whose patients test positive for CMV infection (by either specific histopathology identification or CMV PCR) and are *three times* more likely to undergo colectomy. Therefore, recommendations have been made to enhance the CMV testing service for all IBD patients and in doing so it is envisaged this high risk patient group would have a measurable improvement with significant reduction in the colectomy rate. Further investigation of any reduction in colectomy rate would form the basis of a re-audit. Recommendations are as follows:

1. Develop and disseminate a regional protocol for Histopathology to receive tissue samples for processing for IBD patients.

2. Develop and disseminate a regional protocol and request form on the RVL website listing appropriate test/samples for IBD patients.

3. Develop a regional communication protocol to enable more effective management of specimen transit and result relay for IBD patients.

Clinical audit report

Background/rationale

Cytomegalovirus (CMV) is a member of the Herpesviridae family and is ubiquitous in developed nations with a seroprevalence between 40-70% in the adult population.[3] CMV infection can occur at any stage of life from childhood to late adulthood. In the immunocompetent population, primary CMV infection is generally asymptomatic and resolves to a state of life-long latency. Like all herpesvirus in the latent state, these viruses may reactivate periodically, and with CMV this reactivation is localised to within the colon. Colitis is inflammation of the inner lining of the colon. There are numerous causes of colitis including infection, inflammatory bowel disease (IBD), ischemic colitis, allergic reactions and microscopic colitis. In addition, patients with IBD, including both UC and CD, are known to be at increased risk of colonic reactivation of CMV, due to both the disease process itself, and the use of immunosuppressive therapies. Numerous case reports and retrospective studies have noted increased colonic mucosal CMV replication in IBD patients, and that this may be associated with steroid-refractory flares, a worsening disease prognosis and increased risk of toxic megacolon and subsequent surgical intervention. [4, 5, 6]

This audit explores a cohort of IBD patients (adult and paediatric in-patient and out-patient) over a specified period and also a sub-group within this cohort – those with severe acute colitis (SAC) and/or steroid refractory colitis (SRC). SAC includes those patients with a severe flare of colitis with more than 10 bowel motions per day, continuous abdominal pain and severe toxic symptoms; SRC is a severe form of colitis lacking a meaningful clinical response to steroid treatment after 7 days (oral) or 10 days treatment (IV). This will help to establish the clinical effect of colitis and the presence of the CMV virus in terms of management with antivirals or surgical intervention.

A recent prospective study reported the mortality rate for CMV colitis complicating UC to be as high as 30% and the rate of surgery as 40%.[3,7] CMV has been identified in colonic tissue from 21-34% of patients with severe colitis and in 33–36% of the steroid-refractory sub-group of this patient group.[8] -It is suggested that CMV

replicates in areas of active IBD causing further tissue injury, aggravating the severity of the underlying IBD.[9,10] Further support for this theory comes from studies showing that early antiviral treatment may improve clinical outcome in affected patients[4]. The association between CMV and IBD was first noted in 1961[11] but it remains to be established whether CMV initiates acute exacerbations of IBD or is a consequence of the IBD activity and its treatment.

Current British Society of Gastroenterology (BSG) Guidelines for the management of inflammatory bowel disease in adults[2] state that with severe or refractory colitis initial investigations should '*consider CMV* as *reactivation is common in patients with IBD on immunosuppression. CMV is associated with a poor outcome and high colectomy rate. A combination of colonic histology and PCR for viral DNA confirms the diagnosis rapidly. Immunosuppressants should be discontinued in favour of intravenous Gancyclovir for 2 weeks or the more expensive but equally effective oral Valgancyclovir'*. This is further supported in the European Crohn's and Colitis Organisation (ECCO) consensus statement[12] on prevention, diagnosis and management of opportunistic infections in IBD.

The Regional Virus Laboratory has identified from laboratory records significant inconsistencies in the CMV tests requested for those IBD patients, steroid-refractory or otherwise, and also in the specimen types submitted. Discussion and engagement with consultant gastroenterologists and the regional Northern Ireland IBD Interest Group has resulted in a small retrospective data cohort analysis which supports this observation (presented at the Ulster Society of Gastroenterology 2013 autumn conference). CMV superinfection/reactivation may be underdiagnosed in IBD patients. Owing to the increased morbidity and high colectomy rate reported in cases of CMV colitis, clear guidance and an agreed local policy are required to ensure standardised and effective management of these patients.

Methodology

This retrospective audit included patients from the period January 2010 - March 2013. The audit population was divided into two patient cohorts, a severe acute colitis and/or steroid refractory colitis cohort, and a non-acute IBD cohort.

Clinicians managing IBD were keen to improve the current management of CMV colitis in these patients and believed the best way to do this was through a formal audit with the aim of implementation in time of a regionally agreed laboratory protocol (specimens and test requests) and development of a patient management protocol in relation to CMV colitis.

The audit project team members were proposed at a multidisciplinary Northern Ireland IBD Interest Group meeting in September 2013. This group meets every three months and includes consultant gastroenterologists, consultant surgeons and members of the Crohn's and Colitis UK group. It was agreed to include in the project team a consultant gastroenterologist from each of the five HSC Trusts; laboratory representation in the form of both a consultant virologist and a consultant pathologist (Histopathology); and a lead epidemiologist.

Data were collected by IBD and endoscopy nursing staff from all five HSC Trusts. Staff either volunteered or were nominated at the Northern Ireland IBD Interest Group Meeting. A total of nine nursing staff were involved: BHSCT (4 nurses), SEHSCT (1 nurse), SHSCT (1 nurse), WHSCT (1 nurse) and NHSCT (2 nurses).

Audit Population (n=326)

Patients who had:

- specimen(s) submitted to the Regional Virus Laboratory for CMV PCR testing as [TISSUE/BIOPSY material] or [BLOOD] or [FAECES] Or:
- specimen(s) submitted to the Regional Virus Laboratory *with* supportive, descriptive, clinical information (on received specimen request form) with one of the following diagnoses: [INFLAMMATORY BOWEL DISEASE] [IBD] [CROHNS] [ULCERATIVE COLITIS] [CD] [UC] [ACUTE SEVERE COLITIS] [ASC] [FLARE] [STEROID REFRACTORY COLITIS] [SRC] [COLITIS] [FLARE].

From this audit population the following exclusions were applied:

Exclusion 1: patients (n=30) who had specimens submitted to the Regional Virus Laboratory for CMV PCR as [TISSUE/BIOPSY material] or [BLOOD] or [FAECES] but were not IBD patients and therefore were not included within the IBD patient cohort.

Exclusion 2: patients (n=4) for whom patient notes were not available at the time of data collection.

Exclusion 3: patients (n=15) for whom notes collected on the Access proforma data collection spreadsheet were incomplete.

The sample of IBD Patients to be included in this audit was therefore (n=277*).*
All 277 patients attended one of the five HSC Trusts as either an inpatient or an outpatient on these occasions.

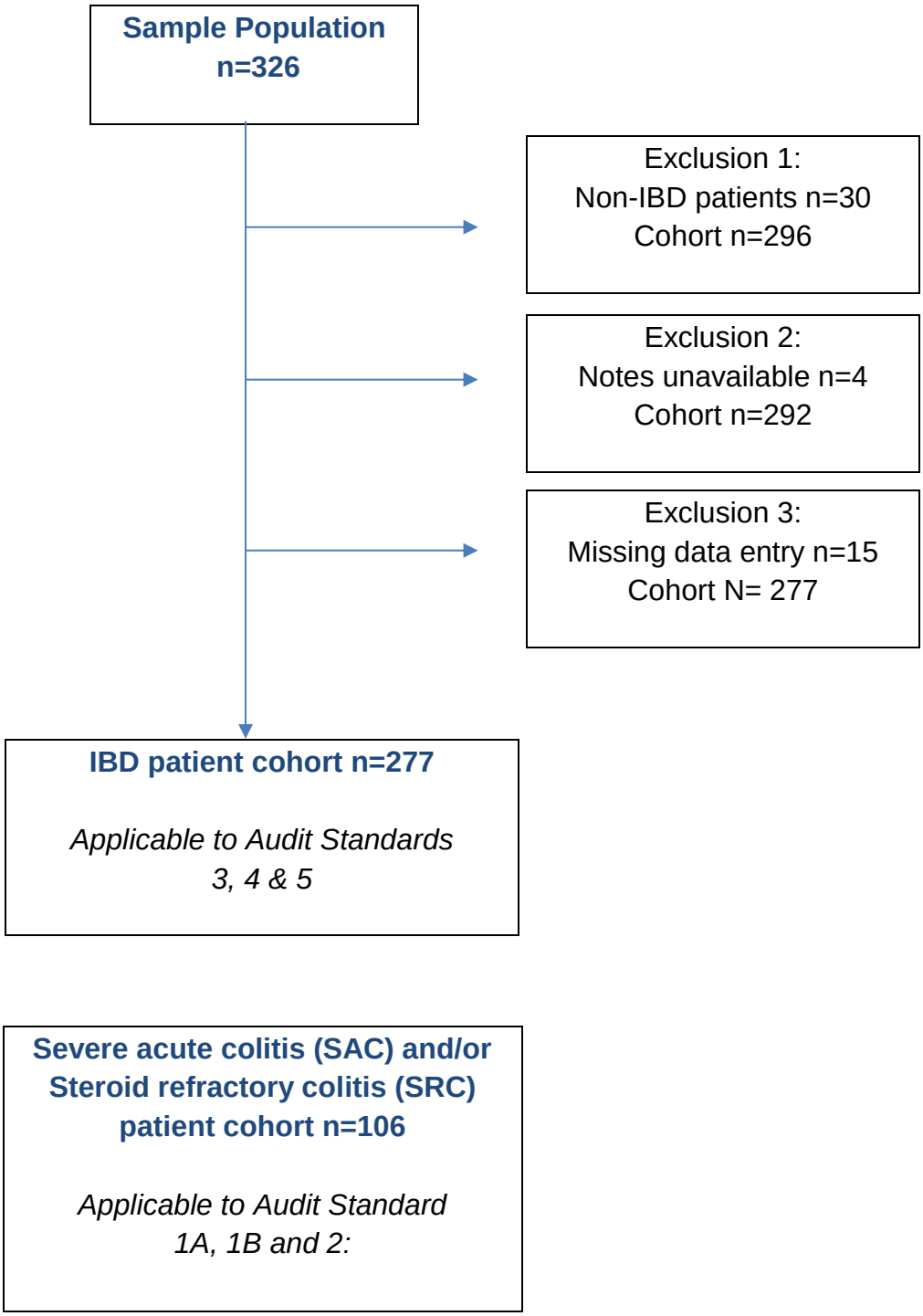
Of the 277 patients a total of 106 were further grouped as SAC/ SRC.

Sub Cohort (n=106) SAC/SRC

Inclusion: These patients were identified from the overall IBD patient Cohort of n=277 as having documented in the Access proforma data collection spreadsheet: tab: Clinical Data Investigations Start Day of IV Steroids' as day 1-10 of admission; they may also have had FLARE or SRC documented on a laboratory request form.

Figure 1: Patient Cohorts

Audit patient cohorts and how they relate to standards 1A, 1B, 2, 3, 4 and 5.



Data collection tool

The data collection tool was piloted during an observational study[1] and further modified from MS Excel to MS Access in readiness for data collection.
(Appendix 1)

Data Source

The data source were a combination of patient notes and laboratory computer systems (Laboratory Information Management System) (LIMs Clinisys LabCentre) providing information for patients who had specimens submitted and received by the Regional Virus Laboratory, Royal Victoria Hospital.

Audit type

This was a retrospective audit which included patients from the time period January 2010 to March 2013.

Data collection

- Retrospective data were collected from patient notes, patient care records and laboratory computer systems (LIMS Clinisys LabCentre).
- Data were collected by IBD/endoscopy nursing staff members from all five HSC Trusts.
- Each data collector had training provided by the audit project lead prior to embarking on note retrieval and data input. The designated nurses from each Trust entered data into five tab fields with drop-down menu options and free-text options: Tab1: Demographics, Tab2: Baseline Clinical, Tab3: Clinical Course, Tab4: Clinical Data Investigations and Tab5: Virology Laboratory Results. These five tabs were designed to collect data/variables from the study population based on 'flare episodes,' to include:
    - patient demographics (age/sex/underlying conditions)
    - baseline therapeutics (e.g. 5-ASA and immunosuppressant therapy)
    - blood test results including albumin and CRP
    - endoscopy findings

- histopathology results
- virology results*
- surgery (colectomy)
- discharge and follow-up

(*Virology results to include specimen type, test request, test result, date of specimen, date of specimen receipt, date of specimen result, and evidence of result communication other than release to LIMs Clinisys LabCentre).

- Data were entered into a password protected MS Access database provided to nominated data collectors in each Trust.

- Data entry was validated by the project lead for 10% of each Trust patient sample by cross referencing to LIMS Clinisys LabCentre and on occasion by recalling patient note files. This was carried out either via site visits or via database retrieval and cross referencing at the BHSCT RVL site.

Data analysis

- The analysis strategy was descriptive with data presented as numbers and proportions.
- The computer system used was MS Access.
- Data analysis was carried out by the project lead, guided by a lead epidemiologist with IT support being provided by Leadership Northern Ireland.

Findings

Descriptive summary of patient cohorts in this audit

IBD patient cohort N=277 as shown in Table 2

Table 2: Demographics of the N=277 IBD cohort

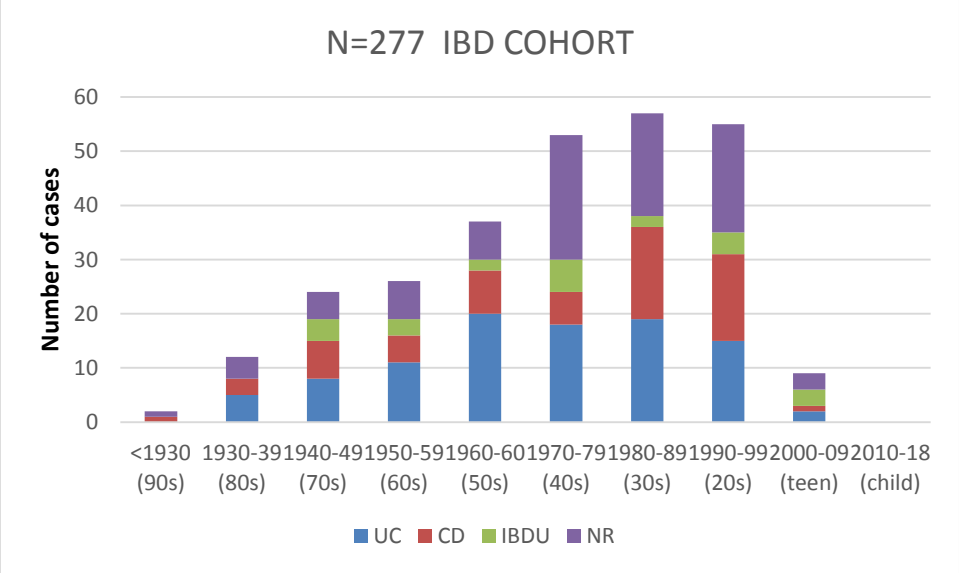
N=277		n	%
Gender	Male	139	50
	Female	138	50
Trust	BHSCT	126	46
	WHSCT	49	18
	NHSCT	42	15
	SHSCT	19	7
	SEHSCT	41	15
Disease distribution	Ulcerative Colitis (UC)	98	35
	Crohn's Disease (CD)	63	23
	IBD Unclassified (IBDU)	24	9
	Not Recorded (NR)#	92	33

#The 'not recorded (NR)' in this cohort reflects outpatients where disease distribution was not accessible for database input.

Table 5 represents the overall sample cohort of inflammatory bowel disease (IBD) patients across all five HSC Trusts. This cohort demonstrates equal gender split and represents a range of IBD patients including ulcerative colitis, Crohn's disease and inflammatory bowel disease unclassified.

Figure 3 illustrates the year of birth with disease distribution in terms of ulcerative colitis (UC), Crohn's Disease (CD), IBD Unclassified (IBDU) and Not Recorded (NR).

Figure 3: Age range of N=277 IBD patient cohort



The age range in figure 3 is wide, from teen years to >90yrs. The highest number of IBD cases is found in adults aged from >20 to <50yr.

Severe acute colitis: SAC/SRC patients N=106

A sub-cohort of the IBD sample (n=277) only included SAC/SRC. Demographics of the N=106 sub-cohort are displayed in Table 3.

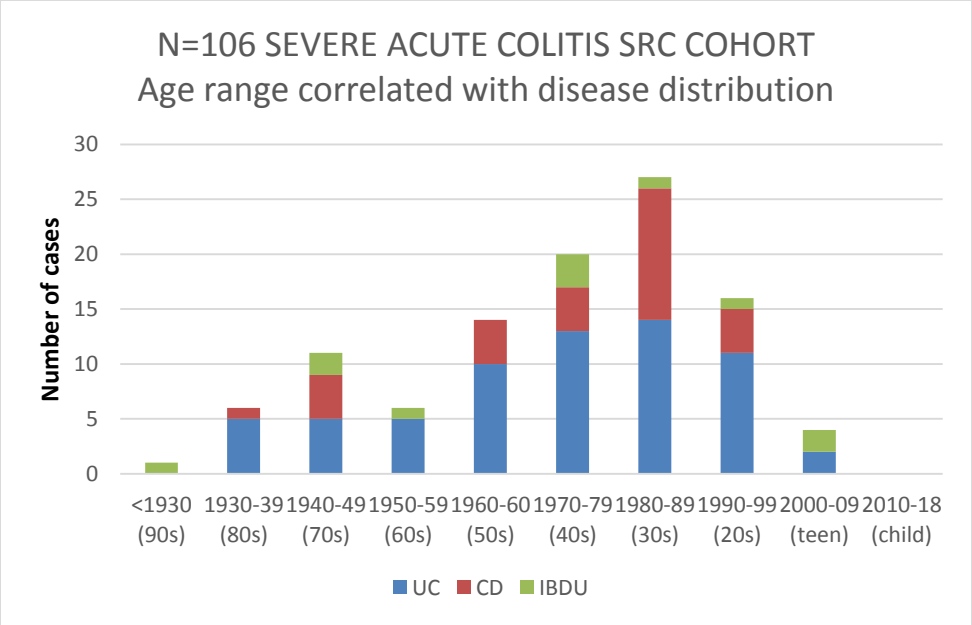
Table 3: Demographics of the SAC/SRC cohort (N=106)

N=106		**n**	**%**
Gender:	Male	53	50
	Female	53	50
Trust:	BHSCT	50	47
	WHSCT	20	19
	NHSCT	10	9
	SHSCT	18	17
	SEHSCT	8	8
Disease distribution:	Ulcerative Colitis (UC)	66	62
	Crohn's Disease (CD)	29	27
	IBD Unclassified (IBDU)	11	10

Table 3 shows the representative sample of SAC and/or SRC in patients across all five HSC Trusts. This cohort demonstrates equal gender split and represents a range of IBD patients including ulcerative colitis, Crohn's disease and inflammatory bowel disease unclassified.

Figure 4 illustrates the year of birth with disease distribution in terms of ulcerative colitis (UC), Crohn's Disease (CD) and IBD Unclassified (IBDU).

Figure 4: Age range of SAC/SRC patient cohort (N=106)



The age range is wide, from teens to >90yr. The highest number of SAC/SRC cases is seen in adults aged 20-40yr.

Audit Standards

The audit standards were applied to the two patient cohorts:

- Standards 1A and 1B were applied to 106 patients (SAC/ SRC cohort)
- Standards 2, 3, 4 and 5 were applied to the full audit sample (N=277) (SAC/SRC (N=106) & Non acute colitis cohort (N=171).

Standards 1A and 3 were assessed for compliance whilst the remaining standards (1B, 2, 4 & 5) established a baseline in these areas.

Standard 1A:

	Target	Compliance
During admission, all IBD patients presenting with severe acute colitis or steroid-refractory colitis to have a colonic biopsy (tissue) specimen submitted for histopathology#. (N=106)	100%	92%

#The Gold Standard for a CMV colitis diagnosis is histopathology investigation based upon the triad of (1) clinical symptoms of gastrointestinal disease, (2) visualisation of characteristic lesions on endoscopy and (3) intranuclear or cytoplasmic inclusions on pathology staining with haematoxylin and eosin (H&E) and with positive immunohistochemistry (IHC) for CMV

Exceptions: None

Compliance*: 92% (*98 of 106)

Non-compliance*:8%* (8 of 106) did not comply with tissue sample submission although 6 of these 8 did have evidence of endoscopy

Interpretation of results

Standard 1A specifically applies to the SAC/SRC patients (n=106) of which 98 (92%) had evidence of tissue sample submission for histopathological examination.

Of the 98 SAC/SRC patients with histopathology, 10 (9%) of samples submitted were histologically positive for CMV.

Standard 1B:

	Target	Achieved
During admission, all IBD patients presenting with severe acute colitis or steroid-refractory colitis to have a colonic biopsy (tissue) specimen submitted to the Regional Virus laboratory for CMV DNA testing via Polymerase Chain Reaction (PCR)#.(N=106).	Baseline	Established baseline 70%

#PCR of CMV DNA in colonic tissue exhibits high sensitivity (92-97%) and specificity (93-99%) when used to diagnose CMV infection and recently the European Crohn's and Colitis Organisation guideline recommend the use of colonic PCR in CMV diagnosis.[13]

Exceptions: *None*

Baseline outcome*: 70% (74 of 106)*

Baseline Non-compliance*: 30% (32 of 106) cases had no record in the audit collection proforma of PCR investigations on colonic tissue.*

Interpretation of results

The standard was assessed using the 106 IBD inpatients identified as SAC/SRC. A total of 74 out of 106 SRC patients had evidence of tissue submission for CMV DNA testing via PCR (baseline of compliance 70%).

Standard 2

Other specimen types can be received by the Regional Virus Laboratory for CMV diagnostic testing, in addition to tissue samples (Standard 1A &1B). These additional specimens can include;

- blood (serum or EDTA Plasma samples) for CMV DNA PCR
- blood (serum) for antibody screening (antibody IgG indicates past infection and latent virus and antibody IgM indicates current active infection)
- faeces for CMV DNA PCR

For Standard 2, the baseline outcome has been established for these additional specimens submitted in the SAC/SRC cohort (n=106)

Standard 2:

	Target	Achieved
Establish a baseline for specimen submission of blood and or faeces to the Regional Virus laboratory (RVL) for CMV virology investigation, and the appropriate laboratory test requests in the SAC/SRC cohort (n=106).	Baseline	Established baseline for specimen receipt: 1. 27%: CMV Blood IgG screening test 2. 50%: CMV Blood IgM screening test 3. 51%: CMV Blood PCR 4. 29%: CMV Faeces PCR

Exceptions: *None*

Baseline outcome:

27% CMV Blood IgG screening test (29 of 106)

50% CMV Blood IgM screening test (53 of 106)

51% CMV Blood PCR (54 of 106)

29% CMV Faeces PCR (31 of 106)

Interpretation of results for blood specimen(s) submitted to Virology for CMV antibody screening:

Of the SAC/SRC patients, 29 of the 106 (27%) had blood specimens submitted for CMV IgG antibody screening of which 19 of the 29 (66%) were test positive; *supporting the suggestion that detectable IgG is useful to indicate potential CMV reactivation and infection.* The positive CMV result from IgG antibody screening is an indication that these patients have undergone CMV reactivation of past CMV infection and not primary infection (first infection with CMV), a result that is common with all herpes viruses.

A total of 53 of the 106 (50%) had blood specimens submitted for CMV IgM antibody screening of which 2 (4%) were test positive. Although the IgM antibody is recognised as an 'acute' antibody response, the window period to detect IgM positivity is narrow and a negative result does not exclude CMV infection. The results from the IgM screening test (4% positive (2 of 53), provides supportive evidence that IgM is not a useful test for CMV diagnosis, with <5% IgM positive.[14]

Interpretation of result from Standard 1A and Standard 1B relating to the CMV IgG and IgM antibody screening test as useful indicators for CMV infection

In relation to standard 1A, a total of 98 of the 106 SAC/SRC patients had CMV histopathology (tissue samples submissions) and of these 10 patients (9%) were positive for CMV. Nine of these 10 patients were also IgG positive (one patient not tested).

Of the 10 histopathology patients who tested positive for CMV, 8 were tested for blood CMV antibody IgM, and of these only one tested positive for IgM, supporting the suggestion that IgM is not a useful test for CMV infection diagnosis.

In relation to standard 1B, a total of 74 of the 106 SAC/SRC patients had tissue CMV DNA PCR investigation; 9 out of 74 (12%) were positive for CMV, and 8 of these 9 patients were also IgG positive (one was not tested), a finding which supports the hypothesis that IgG is useful to indicate potential CMV infection.

Of the 9 tissue PCR patients who tested positive for CMV, 6 were tested for blood CMV antibody IgM, and of these only one tested positive for IgM, supporting the suggestion that IgM is not a useful test for CMV infection diagnosis.

Interpretation of results for additional specimens submitted to Virology for CMV PCR screening (blood and or faeces):

Of the SAC/SRC patients, 54 of the 106 (51%) had blood submitted for CMV DNA PCR, of which 8 (15%) were test positive. A total of 31 of the 106 (29%) had faeces submitted for CMV DNA PCR, of which one (3%) was test positive.

The majority 94% (99 out of 106 SAC/SRC patients), had a record of CMV DNA PCR in specimen tissue *or* blood *or* faeces. Of these, 74 (as in standard 1B) had submitted tissue for CMV DNA PCR and therefore 25 submitted other specimen(s) (blood, faeces, or both blood and faeces samples) only for CMV DNA PCR.

Standard 3

	Target	Compliance
Upon confirmation of CMV colitis via a combination of colonic histology and/or PCR, patients should be treated with antivirals (either Ganciclovir or Valganciclovir) for a total of 14-21 days if appropriate (N=277)	100%	37%

Exceptions: *None*

Compliance*: 37% (15 of 41)*

Non-compliance*: Fifteen out of 41 (37%) CMV positive patients (confirmed by PCR and or histopathology) had a record of antiviral treatment in the form of either Ganciclovir or Valganciclovir. Duration of treatment could be calculated for 12 of these patients.*

Interpretation of results

Table 4 shows the breakdown of the sample cohort of all IBD patients (n=277), 41 had confirmation of CMV colitis (16 out of 106 of the SAC/SRC sample cohort, and 25 out of 171 of the non-severe acute colitis cohort (any combination of CMV PCR with/without positive CMV histopathology).

A total of 13 out of 16 (81%) of the SAC/SRC CMV positive patients had received antiviral treatment, and 2 out of 25 (8%) of the non-severe acute CMV positive patients had a record of antiviral treatment, with either Ganciclovir or Valganciclovir. Fifteen out of 41 (37%) of the CMV positive patients (confirmed by PCR and/or histopathology) had a record of antiviral treatment.

The duration of drug treatment was available for 12 CMV positive patients with a treatment duration range of 3–30 days (median = 12 days).

Table 4: Breakdown of CMV colitis positive patients and anti-viral treatment recorded

	Sample breakdown	**CMV positive**	**Anti-viral treatment either Ganciclovir or Valganciclovir**
SAC/SRC sample cohort	106	16*	13 of 16
Non-severe acute colitis cohort	171	25*	2 of 25
IBD total sample	277	41*	15 of 41

*any combination of CMV PCR with/without positive CMV histopathology

Standard 4:

	Target	Achieved
Establish if a protocol for rapid communication (by telephone to requestor) of virology laboratory results is in place to enable timely initiation of antiviral therapy where possible (Positive CMV PCR results in the IBD cohort (34 of 277).	baseline	Established baseline: 50% (positive CMV PCR results telephoned to requestor)

Exceptions: *None*

Baseline Outcome*:* 50% positive CMV PCR results telephoned to requestor

Turn-around time (TAT) for virology results

The turn-around-time (TAT) of results was assessed in the CMV PCR positive patients (n=34) from the IBD patient cohort (N=277). The audit has established that there is no agreed protocol to telephone or communicate results rapidly to the requestor. The current system relies on the patient being identified by chance as 'IBD' at the point of the result being issued and the laboratory making telephone contact with the issuing requestor to relay the results.

A total of 41 patients were tissue CMV positive in the 277 IBD cohort (7 of these results were only histopathology positive for CMV and TAT data were not available for inclusion in this standard analysis). Therefore a total of 34 patients had a positive CMV PCR result issued from the RVL. Of the 34 patients, 17 (50%) had positive CMV PCR results telephoned to the requestor (Table 5).

There was no evidence on the laboratory information management system (LIMs Clinisys LabCentre) to indicate that a telephone call or communication had been received by the laboratory as notification of the specimen being sent.

Table 5: Turn-around Time (TAT) as calculated from receipt of sample to result issue (N=34 positive results)

Turn-around-time from sample receipt to result issue	Sample number	Details Positive CMV PCR	Phoned n=17
<24 hrs	*3*	*2x Blood PCR* *1x Tissue PCR*	*Not Phoned* *1x Phoned*
24hrs - ≤48hrs	*15*	*4x Blood PCR* *11x Tissue PCR*	*2x Phoned* *6x Phoned*
>48hrs	*16*	*3x Blood PCR* *13x Tissue PCR*	*1x Phoned* *7x Phoned*

The Microbiology User Manual provided to users of the laboratory service states the expected TAT of ≤48 hours for fresh tissue specimens and up to 5 days for FFPE tissue (non-fresh wax embedded tissue specimens). There were no records in the LIMs system to determine if the tissue specimen was fresh or FFPE.

Interpretation of results

A total of 34 patients had a positive CMV PCR result issued from the RVL; 17 patients had these results telephoned to the requestor and 17 did not. Of those (n=17) whose results were telephoned to the requestor, ten patients received antiviral drug treatment (either Gancyclovir and/or Valganciclovir), and it was noted that the date of the results telephoned to requestors typically corresponded with commencement of antiviral drug treatment. Of the seven remaining patients, none of these received antiviral treatment and none of these patients progressed to colectomy.

For the ten patients who received antiviral treatment, two of these progressed to colectomy; one of these patients had undergone colectomy before their result was telephoned and one underwent colectomy following six days of antiviral drug treatment. The remaining eight patients that received antiviral treatment did not progress to colectomy.

Table 6 provides further details of the 17 patients who had results telephoned to the requestor and the bullet points below provide descriptions for the headings recorded on Table 6:

- **Transit:** specimen 'transit' time (specimen date to date of receipt)
- **TAT:** turn-around time from receipt of sample to result issued
- **W/E:** if the specimen was received to test over a weekend
  (If this is indicated as a Yes in Table 6 this automatically delays the testing of the specimen)
- **Tx GCV & Tx VGCV:** whether the patient was treated with antiviral drugs (Ganciclovir (GCV) and or Valganciclovir (VGCV))
- **Colectomy:** whether a colectomy was performed

Table 6: Details of the 17 patients who had results phoned to requestor

Audit ID	*Transit*	*TAT*	*W/E*	*Tx GCV*	*Tx VGCV*	*Colectomy*
4	24Hrs	24Hrs	NO	YES	YES	NO
21	3Days	24Hrs	NO	YES	NO	YES
22	24Hrs	48Hrs	NO	NO	NO	NO
28	3Days	>48Hrs	YES	NO	NO	NO
30	3Days	>48Hrs	YES	NO	NO	NO
31	48Hrs	24Hrs	YES	YES	NO	NO
50	24Hrs	>48Hrs	YES	YES	YES	NO
52	48Hrs	>48Hrs	NO	NO	NO	NO
61	24Hrs	>48Hrs	NO	NO	NO	NO
80	3Days	48Hrs	NO	YES	YES	NO
98	24Hrs	48Hrs	NO	YES	NO	YES
140	24Hrs	24Hrs	NO	YES	YES	NO
172	24Hrs	>48Hrs	YES	NO	YES	NO
249	<24Hrs	>48Hrs	YES	YES	YES	NO
250	24Hrs	48Hrs	NO	YES	YES	NO
253	24Hrs	48Hrs	NO	YES	NO	NO
316	48Hrs	4Days	NO	NO	NO	NO

Table 7 provides details of the 17 patients (from 34 patients with a positive CMV DNA PCR result) who did NOT have had results telephoned to requestor and of these;

- thirteen patients were treated with antiviral drugs and three patients progressed to colectomy.
- four patients were not treated with antiviral drugs and one of these patients progressed to colectomy.

Of note, the transit date of results provided to the requestor was typically the date antiviral treatment started

The data from the four colectomy patients whose results were NOT telephoned was further analysed and identified that;

- 1 patient progressed to colectomy 7 days after specimen date, 3 days after results were issued and 5 days after antiviral treatment
- 1 patient progressed to colectomy 6 days after specimen date, 6 days after results were issued and 8 days after antiviral treatment
- 1 patient progressed to colectomy 9 days after specimen date, 7 days after results were issued and no start date on antiviral treatment was available
- 1 patient had a colectomy 3 days after specimen date, 2 days BEFORE results were issued and with no antiviral treatment

It was also noted that;

- 2 of 4 patients had started antivirals before a result was issued to the LIMs system.

Table 7 provides further details of the 17 of the 34 positive CMV DNA PCR results NOT telephoned to the requestor. Of note: Those with longer ***Transit*** times were not restricted to tertiary hospitals.

Table 7: Details of the 17 patients whose results were NOT phoned to requestor

Audit ID	*Transit*	*TAT*	*W/E*	*Tx GCV*	*Tx VGCV*	*Colectomy*
5	48Hrs	48Hrs	NO	YES	YES	YES
6	24Hrs	<24Hrs	NO	YES	NO	NO
7	<24Hrs	>48Hrs	YES	YES	YES	NO
8	24Hrs	24Hrs	NO	YES	YES	NO
25	4Days	>48Hrs	YES	NO	NO	NO
29	24Hrs	24Hrs	NO	YES	NO	NO
34	24Hrs	24Hrs	NO	YES	YES	NO
49	4Days	24Hrs	NO	NO	NO	YES
51	24Hrs	48Hrs	NO	YES	YES	NO
53	48Hrs	>48Hrs	YES	NO	NO	NO
54	24Hrs	48Hrs	NO	YES	YES	NO
55	24Hrs	>48Hrs	YES	NO	NO	NA
71	24Hrs	>48Hrs	YES	YES	NO	YES
97	24Hrs	>48Hrs	YES	NO	YES	NO
247	<24Hrs	>48Hrs	NO	YES	YES	NO
248	24Hrs	>48Hrs	YES	YES	YES	YES
251	24Hrs	24Hrs	NO	YES	YES	NO

Standard 5:

	Target	Achieved
Establish a baseline of surgical intervention in the form of a colectomy in CMV positive IBD patients (total 211 out of 277) (91 of 106 SAC/SRC, and 120 of 171 of the non-acute IBD cohort)	Baseline	Established baseline: 1. 28%: Colectomy rate in SAC/SRC Cohort 2. 50%: Colectomy rate in CMV positive SAC/SRC cohort 3. 4%: Colectomy rate in non-acute IBD Cohort 4. 6%: Colectomy rate in CMV positive non-acute IBD patients

Exceptions: *None*

Baseline Outcome:

Colectomy rate in SAC/SRC cohort - 28% (25 of 91)

Colectomy rate in CMV positive SAC/SRC cohort - 50% (6 of 12)

Colectomy rate in non-acute IBD cohort - 4% (5 of 120)

Colectomy rate in CMV positive non-acute IBD cohort - 6% (1 of 18)

This standard assesses the whole cohort n=277; however, 66 patients are not included as they either had no colectomy status recorded or had a colectomy performed outside this audit period. This standard also looks specifically at the sub cohort of SAC/SRC (N=106).

1. Severe acute colitis (SAC) and/or steroid refractory colitis (SRC) cohort

A total of 104 out of 106 patients in this cohort had their colectomy status recorded. In the SAC/SRC cohort (n=104), a total of 13 patients had a colectomy which was either pre-audit episode (n=1) or post audit episode (n=12). The colectomy rate at the time of the recorded episode/investigation for CMV was 25 out of 91 (28%); 66 did not have a colectomy.

A total of 12 of the 91 patients were CMV positive. Of these, 10 were treated with antivirals (83%) (either Ganciclovir or Valganciclovir).

The odds of colectomy were three times higher in those who were CMV positive (Odds ratio 3.16, 95% CI (0.74, 13.21; P=0.06)) however this is not statistically significant as the lower confidence limit is less than one. Please note that univariate analysis is NOT adjusted for other factors which may influence colectomy rate). (Table 8)

Table 8: SAC/SRC colectomy outcome vs CMV status

Data recorded on colectomy status	Colectomy in this episode	No Colectomy in this episode
CMV pos[#] n=12	6 (5x antivirals 83%)	6 (5x antivirals 83%)
CMV neg n=79	19	60
N= 91	N=25	N=66

[#]CMV positive by PCR and/or histopathology

2. Non-acute IBD Sub-group (N=171)

A total of 154 out of 171 patients in this cohort had their colectomy status recorded. In this non-acute IBD cohort (n=154), a total of 34 had a colectomy either pre-audit episode (n=5) or post audit episode (n=29). The colectomy rate at the time of recorded episode/investigation for CMV was 5 out of 120 (4%), 115 did not have a colectomy.

A total of 18 of the 120 (15%) non-acute IBD patients were CMV Positive. Of those 18 CMV positive patients, 2 were treated with anti-viral drugs (11%), and 1 had a colectomy (6%).

Table 9 shows a comparison between the CMV positive patients in the non-severe acute colitis cohort, of which 6% had a colectomy during the audit period with the CMV negative patients in this cohort of which 4% had a colectomy. Results showed no statistical significance. Of all the CMV positive patients in this cohort (n=18), 11% (2/18 were given either Ganciclovir or Valganciclovir). The overall colectomy rate in

this non-severe acute colitis cohort at the time of the recorded episode of CMV was 4%.

Table 9 shows the IBD cohort with data recorded on colectomy status, compared to recorded CMV status (PCR and/or histopathology). (Odds ratio 1.44, 95% CI (0.03, 15.72; P=0.75) NB Univariate analysis NOT adjusted for other factors which may influence colectomy rate.

Table 9: IBD cohort with data recorded on colectomy status

Data recorded on colectomy status	Colectomy in this episode	No Colectomy in this episode
CMV pos[#] n=18	1(1x treated 100%)	17 (1x treated 6%)
CMV neg n=102	4	98
N=120	N=5	N=115

[#]CMV positive by PCR and/or histopathology

As an observation on the data obtained for standards 4 and 5, it could be asked if those with a CMV positive PCR result NOT phoned were less likely to commence antiviral drug treatment, or were at increased risk of requiring surgical intervention/colectomy. To address this, patients for whom there was a record of telephoned CMV PCR results had anti-viral treatment and/or colectomy outcome were specifically examined (Table 10A & Table 10B). These are small numbers and there has been no adjustment for confounding factors e.g. co-morbidities or markers of infection.

Table 10A: Treatment with antivirals (Y/N) according to whether or not CMVresult was phoned to requestor

	Treated antivirals	Not treated antivirals
Telephoned	8 (40%)	5 (56%)
Not telephoned	12 (60%)	4 (44%)
Total	20	9

There was no difference in the odds of being treated with antivirals for those where a result was phoned through compared to those without a call.

Table 10B: Colectomy (Y/N) according to whether or not CMV PCR result was phoned through

	Colectomy (Yes)	No Colectomy
Telephoned	2 (33%)	11 (48%)
Not telephoned	4 (67%)	12 (52%)
Total	6	23

There was no difference in the odds of receiving a colectomy for those where a result was phoned through compared to those without a call (odds ratio 0.55, 95% CI (0.04 – 4.82; P=0.66)).

Areas for improvement

This audit, through assessment of standards, established a number of areas for improvement and possible re-audit. Areas for improvement include the selection of the most clinically useful tests to establish if there is current CMV infection in the IBD patient. Evidence has also been presented of the correct specimen type being essential to delivering clinically relevant results. An issue highlighted within this audit is the need for better communication protocols between pathology laboratories (virology and histopathology) and the health professional, to ensure timely and effective management of any identified CMV infection.

Discussion

This audit addressed the important and common condition of severe acute colitis in patients with inflammatory bowel disease (IBD), when complicated by the less well understood condition of CMV colonic mucosal reactivation during an acute episode. Management of acute inflammation in IBD usually relies on treatment with steroids, while CMV colitis requires reduction of immune suppression and the use of antivirals. This treatment conflict is normally handled by a practical approach which checks for evidence of CMV by histology or CMV PCR in tissue biopsies from patients not responding to steroids – (non-response to steroids referred to as 'Steroid Refractory Colitis' (SRC)).

Where CMV is detected, the option of reducing immune suppression and starting antivirals should be considered. Since treatment of acute viral infection is improved by early initiation, optimisation of this approach needs a close working relationship between laboratories and clinical teams to ensure the availability of timely results to guide treatment options. This audit assessed the efficiency of this diagnostic relationship and how tests are requested and results reported.

The audit involved the five HSC Trusts managing patients with IBD with severe acute colitis, and aimed to identify and assess the practices in relation to patient focused test requesting, result reporting and result interpretation in terms of CMV laboratory investigation.

In 2011, a pilot observational study consisting of collating and comparing the type of CMV laboratory investigations performed, and assessing the therapeutic management of CMV and surgical intervention (colectomy rate) in a small cohort (n=30) of IBD patients was carried out and subsequently presented at the USG meeting in the autumn of 2013.[1] This pilot study was undertaken as there was a lack of clarity in available clinical guidance on how to identify CMV in IBD patients, particularly those with SAC or those with SRC.[4] There was also a lack of direction on the type of specimen to submit for laboratory diagnosis and also in the clinical interpretation of the laboratory results.

Standards 1A, 1B and 2 were applicable to the SAC/SRC cohort of patients (n=106). Evidence of tissue submission to both histopathology and virology laboratories for CMV investigation was assessed. A total of 9% of all samples submitted to histopathology were CMV positive, with PCR positive tissue results being found in 12% of cases. These findings support correlation of the gold standard histopathology for CMV diagnosis with tissue CMV DNA PCR procedures. The most interesting finding was the usefulness of tissue CMV DNA PCR and blood IgG screening tests. However, it was evident that all other specimen types for PCR (namely blood and faeces) and serological IgM screening tests are not clinically useful as results are often negative due to the nature of CMV localisation of infection, and the short window period of positivity for CMV IgM. These blood/faecal PCR requests and IgM antibody requests can be regarded as diagnostically supportive rather than definitively diagnostic. These findings are supported by a recent publication by Beswick et al, which concludes 'that primary infection is exceedingly unlikely to cause CMV colitis even in immunosuppressed hosts… a diagnosis of concurrent CMV colitis can be *excluded* in those who are CMV IgG negative'.[14] The authors went on to discuss the usefulness of blood and faeces PCR testing, concluding that blood/serum CMV PCR can be considered as '.an adjunct, but not a replacement, for intestinal CMV diagnosis.. and as yet requires establishment of a quantitative result cut-off; and that further validation is required before faeces could be regarded as clinically applicable'.[14] Of 53 out of 106 samples submitted for CMV IgM testing, two (4%) were positive. This provides further evidence that IgM is not a useful test for CMV diagnosis, with approximately <5% being IgM positive.[14 &15]

Standard 3 focused on antiviral drug treatment and applied to all 277 patients in the IBD cohort. This data showed a low rate of antiviral treatment initiation in these positive patients with 15 out of 41 (37%) documenting antiviral treatment. Antiviral treatment regimens were found to be not standardised in terms of treatment duration. Drug treatment data were available for 12 CMV positive patients, and showed a range of 3 to 30 days with a median of 12 days.

Standard 4 examined the virology laboratory turn-around time for CMV positive result returns. The audit established no protocol currently exists to ensure timely return of CMV DNA PCR results. The current system relies on the patient being identified by as 'IBD' at the point of the result being issued by specimen source information (i.e. gastroenterology origin) or sample type (i.e. tissue for CMV) and the laboratory making telephone contact with the issuing requestor to relay the results. This finding, together with a complete absence of alerting the receiving laboratory to the sending of an urgent sample for processing, leads to unacceptable result turn-around time, often well beyond the stated 48 hours set out in the microbiology user manual. It was also found that specimen receipt at a weekend can lead to unacceptable turn-around times due to the laboratory not offering a seven day testing service at the time of data capture for this audit. It should be noted that a seven day service has been operational since September 2016.

Standard 5 examined the data in relation to antiviral drug treatment and colectomy records; differences were observed in the SAC/SRC cohort (n=106) compared to the non-acute patient cohort (n=171). In the SAC/SRC cohort the odds of having a colectomy were three times higher in those who were CMV positive compared to those who were CMV negative (Odds ratio 3.16, 95% CI (0.74, 13.21; P=0.06). Results also show that 83% of CMV tissue (histopathology and/or PCR) positive patients in this SAC/SRC cohort were treated with antivirals (ganciclovir and or valganciclovir). The overall colectomy rate in this SAC/SRC cohort at the time of the recorded episode of CMV was 28%, with an additional 12 patients in this cohort requiring a colectomy at a future episode. This finding of patients being three times more likely to have colectomy if they have SAC/SRC ***and*** are CMV positive should prompt further investigation to establish the best management of CMV in this cohort with the aim of reducing the colectomy rate.

Of the CMV positive patients in the non-severe acute colitis cohort, 5% had a colectomy; whereas of the CMV negative patients in this cohort 4% had a colectomy. 11% of CMV tissue positive patients were treated with antivirals (ganciclovir and or valganciclovir). The overall colectomy rate in this non-severe acute colitis cohort at the time of the recorded episode of CMV was 4%, yet a further 29 patients went on to have a colectomy at a future date, possibly as a result of progression to SAC/SRC

presentation. These findings may reflect the difference in inpatient and outpatient presentation of 'non-severe acute colitis' although this has not been looked at statistically in this audit.

There was a missed opportunity to assess the effect of stopping of immune-suppressive therapy in favour of initiating antiviral therapy upon a CMV diagnosis. This is therefore a recommendation for further study. Those patients treated with antivirals from both the SAC/SRC and the non – acute cohorts could be further investigated retrospectively to determine the treatment protocol followed. Further work could also be done to compare the level of positivity in CMV DNA PCR results (quantitative) with the treatment protocol and patient outcome.

Learning points

Linked to result reporting, when a positive CMV result is reported back to the ward, the clinical decision taken about reducing immune suppression and/or starting antivirals is complex and not clearly supported by a hard evidence base. However, the consequences of *not* treating a potentially treatable CMV infection (as a result of the conflicting approaches mentioned above) needs to be assessed on a case by case basis.

For clarification, a measure of the significance of a positive CMV PCR result might be helped by how the result is reported and classified. For example, a patient with a combination of (1) a strongly positive tissue CMV DNA PCR result (CMV load > 10^6 IU/ml) with (2) positive CMV H&E and (3) positive CMV IHC would be much more likely to be considered to have a significant infection in need of antiviral treatment intervention than a patient with (1) a low positive tissue CMV DNA PCR result (CMV load 10^3 IU/ml) with (2) H&E negative and (3) IHC negative. It would be useful to devise a method to easily quantify a result to convey this difference in clinical significance which could also be used to help with clinical decision making. This is an area for improvement as it is an achievable goal to provide an agreed scoring system for CMV, inclusive of both the histopathology and virology result. A recent review 'Toward an Algorithm for the Diagnosis and Management of CMV in Patients with Colitis' parallels the findings described in this audit in terms of type of specimen

to be investigated and the need for stratified result interpretation. [14] Assessing the TAT and use of antivirals, but not a scoring system were addressed in this audit. Deficiencies in TAT were recorded which suggested a systems failure, resulting from lack of (a) predefined TATs or (b) measurements of TAT performance. The use of antivirals was also recorded but not the decision-making process itself. Both aspects showed scope for improvement which the audit has addressed. A clinical guide for the review of antiviral treatment and assessing its duration is required.

Observations

Through analysis and reporting of this audit observations have been identified.

Within the data collection proforma a data collection gap was identified and a total of 90 patients (Table 2 IBD patient cohort) had no recorded disease description. This is due to a design error in the data collection proforma utilised and that data collectors were not prompted to record information for outpatients as well as inpatients in relation to disease description.

The population in question has been identified from virology laboratory testing records. It is likely that additional IBD patients exist within health care systems that have not been investigated or managed as IBD patients. This means that no virology laboratory tests will have been performed on these patients and therefore they were not included in the audit sample. This could also mean IBD patients have not had any virological investigation and will not exist in the virology laboratory testing records so cannot be included.

SAC/SRC patients have been grouped together for the purpose of this audit.
There was insufficient retrievable data in relation to antiviral drug treatment i.e. intravenous versus oral and or dosage and duration. This information would further help in understanding the management of CMV within the five HSC Trusts. Therefore, this audit cannot be as helpful as previously hoped in the establishment of Regional Guidance on Antiviral Intervention in IBD.

Recommendations

This audit has identified the need to define test requesting protocols (optimal sample required (e.g. tissue and blood), optimal test requests (e.g. IgG and PCR), and timeliness in both test request and result reporting. The audit has identified a 'high risk patient group', (those patients with severe acute colitis and/or SRC patients) which test positive for CMV infection (by either specific histopathology identification or CMV PCR). The audit has demonstrated that patients in this cohort are *three times* more likely to undergo colectomy. Therefore recommendations have been made to enhance the CMV testing service for all IBD patients and in doing so it would be envisaged this high risk patient cohort would show a measurable improvement with a reduction in the identified colectomy rate. Assessing this possible improvement would subsequently provide the basis of a re-audit. Recommendations are as follows:

1. Develop and disseminate a regional protocol for Histopathology to receive tissue samples for processing on IBD patients.
2. Develop and disseminate a Regional protocol and request form on RVL website listing appropriate test/samples for IBD patients.
3. Develop a Regional communication protocol to enable the more effective management of specimen transit and result relay for IBD patients.

References

1. Vishwa Kalansooriya Pilot data presented at the Ulster Society of Gastroenterology 2013 Autumn Conference.

2. Guidelines for the management of inflammatory bowel disease in adults. Mowat C., Cole A., Windsor A. et al. Gut (2010) http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd_2011.pdf

3. Cytomegalovirus reactivation in ulcerative colitis patients. Nguyen M., Bradford K., Zhang X. And Shih D.Q. Ulcers 2011, id 282507, 1-7 (2011)

4. Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease. Garrido E., Carrera E., Manzano R. And Lopez-Sanroman A. World j Gastroenterol; 19 (1): 17-25 (2013)

5. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. Domenech E., Vega R., Ojanguren I. et al. Inflamm Bowel Dis; 14 (10): 1373-1379 (2008)

6. Prevalence of cytomegalovirus infection in severe refractory ulcerative and Crohn's colitis. Cottone M., Pietrosi G., Pecoraro A., Oliva L. et al. Am J Gastroenterol; 96 (3): 2413-2418 (2001)

7. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. Kishore J., Ghoshal U., Ghoshal U. et al. J Med Micro; 53: 1155-1160 (2004)

8. Cytomegalovirus colitis complicating inflammatory bowel disease. Kandiel A., and Lashner B. Am J Gastroenterol; 101: 2857-2865 (2006)

9. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? Lawler G. And Moss A.C. Inflamm Bowel Dis; 16 (9): 1620-1627

10. The pathogenicity of cytomegalovirus in inflammatory bowel disease, a systemic review and evidence-based recommendations for future research. Hommes D.W. Sterringa G., van Deventer S.J.H. et al. Inflamm Bowel Dis; 10 (3): 245-250

11. Cytomegalovirus inclusion disease and ulcerative colitis; report of a case in a young adult. Powell R.D., Warner N.E., Levine R.S. et al. Am J Med; 30: 334-340 (1961)

12. European evidence based consensus on the prevention and management of opportunistic infections in inflammatory bowel disease. Rahier J.F., Ben-Horin S., Chowers Y. et al. Journal of Crohn's and Colitis (2009) https://www.eccoibd.eu/images/6_Publication/6_3_ECCO%20Guidelines/OI_ECCOconsensus.pdf

13. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Rahier J.F., Ben-Horin S., Chowers Y. et al J Crohn's Colitis; 8: 443-468 (2014)

14. Toward an Algorithm for the Diagnosis and Management of CMV in Patients with Colitis. Beswick L., Ye B., van langenberg D.R. Inflamm Bowel Dis; 22: 12; 2966-2976 (2016)

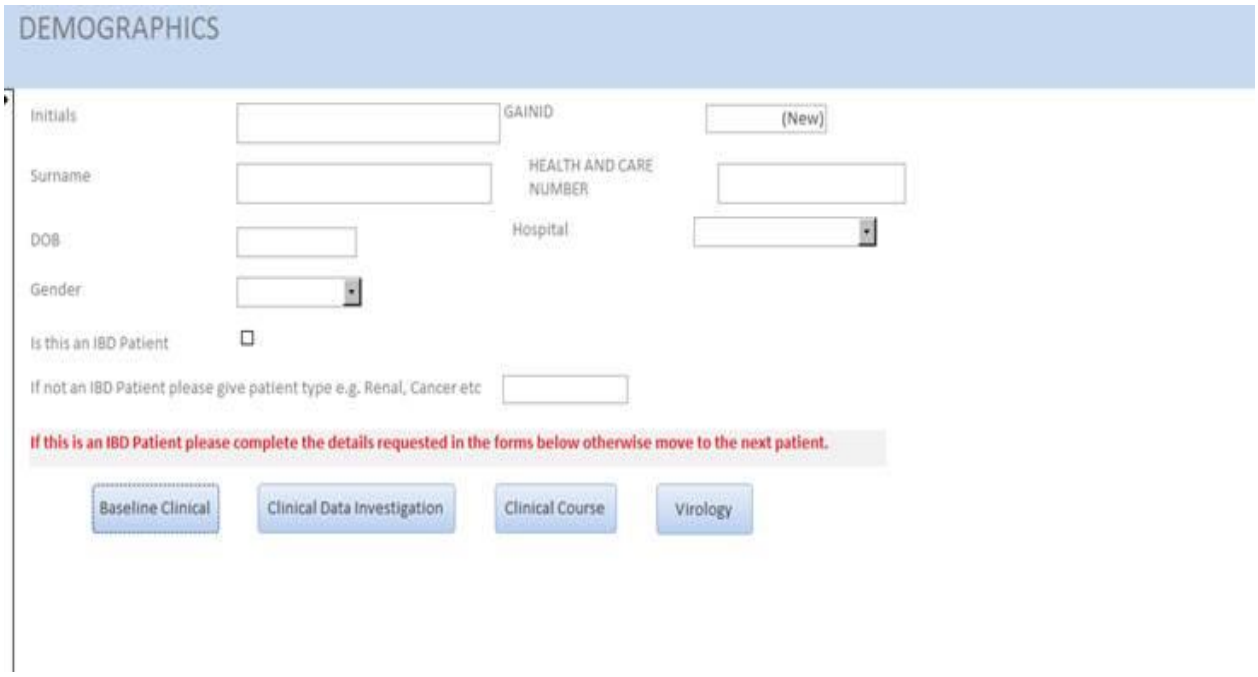
15. Management of CMV infection in IBD Do Carmo AM Pillet S. et al. PLoS one 2014;9:e111574, Dig Liver Dis; 44; 541-548. (2012)

Project Team

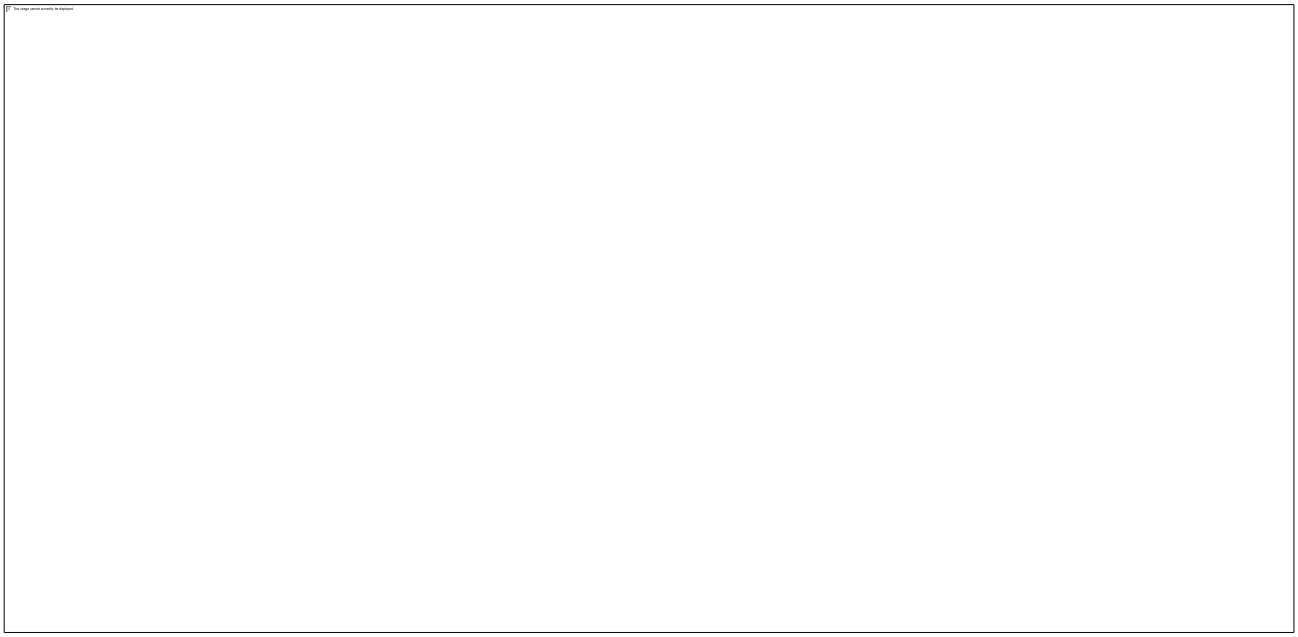
Name	Job Title/Speciality	Trust	Role within Project
Project Lead			
Dr Susan Feeney	Clinical Scientist Virology	BHSCT	Project Lead : Data collection/analysis/report writing
External Reviewer			
Prof Peter Coyle	Consultant Virologist	Hamas General Hospital, Doha, Qatar	Guidance for project development and report reviewer
Project Team			
Dr Seamus Murphy	Consultant Gastroenterologist	SHSCT	Guidance for project development/clinical assessment & assignment of IDB patients into audit. Discussion and implementation of relevant recommendations
Gr Graham Turner	Consultant Gastroenterologist	BHSCT	Discussion and implementation of relevant recommendations
Dr Paul Kelly	Consultant Pathologist	BHSCT	Discussion and implementation of relevant recommendations
Dr Peter Watson	Consultant Gastroenterologist	BHSCT	Discussion and implementation of relevant recommendations
Dr Tony Tham	Consultant Gastroenterologist	SEHSCT	Discussion and implementation of relevant recommendations
Dr George Jacob	Consultant Gastroenterologist	NHSCT	Discussion and implementation of relevant recommendations
Dr Graham Morrison	Consultant Gastroenterologist	WHSCT	Discussion and implementation of relevant recommendations
Dr Lynsey Patterson	Senior Epidemiological Scientist	Public Health Agency	Data analysis/supervision. Epidemiological input into the development of the clinical data collection prorfoma and audit write up

Data collection			
Heather Lawther	Nurse	BHSCT	Data collection and input
Allison Lloyd	Nurse	BHSCT	Data collection and input
Helen Graham	Nurse	BHSCT	Data collection and input
Martina Kelly	Nurse	BHSCT	Data collection and input
Ruth Hall	Nurse	SHSCT	Data collection and input
Gayle Martin	Nurse	SEHSCT	Data collection and input
Patricia Mailey	Nurse	WHSCT	Data collection and input
Jackie Kearns	Nurse	NHSCT	Data collection and input
Louise Scullion	Nurse	NHSCT	Data collection and input

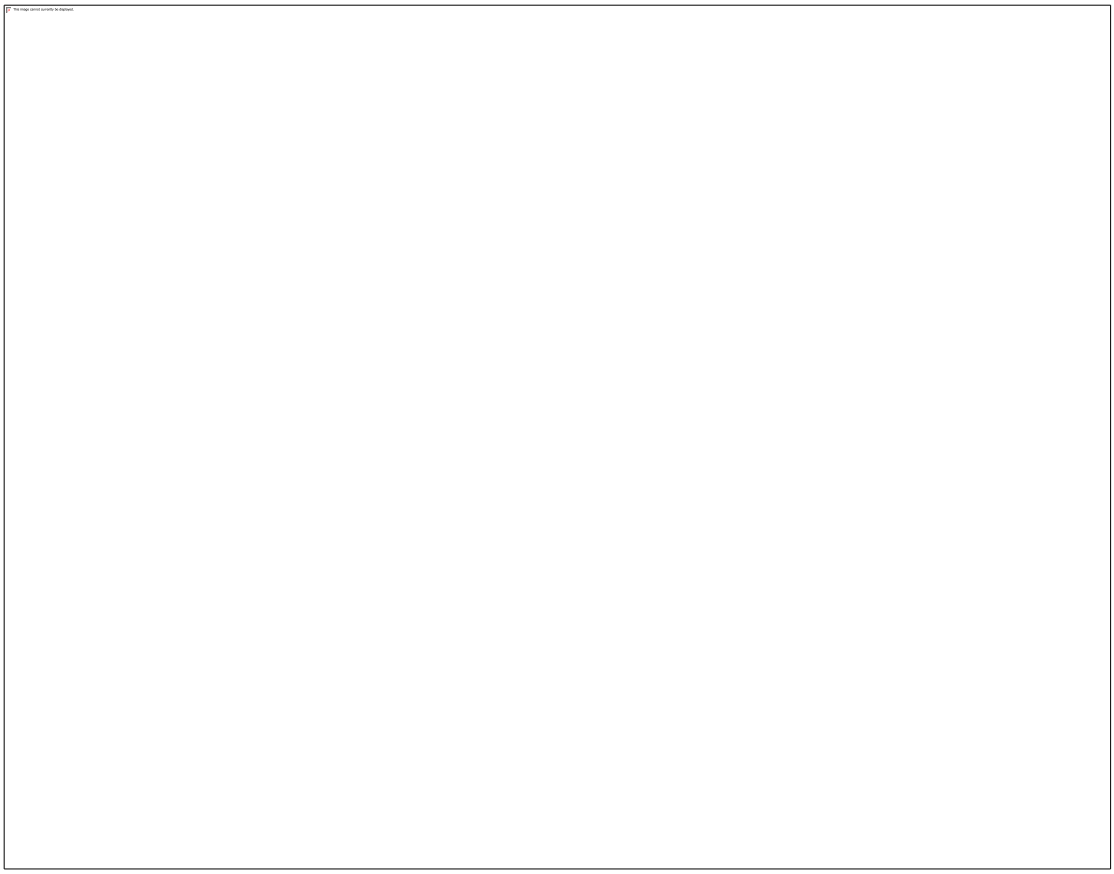
Appendix 1: Audit data collection proforma screen shots



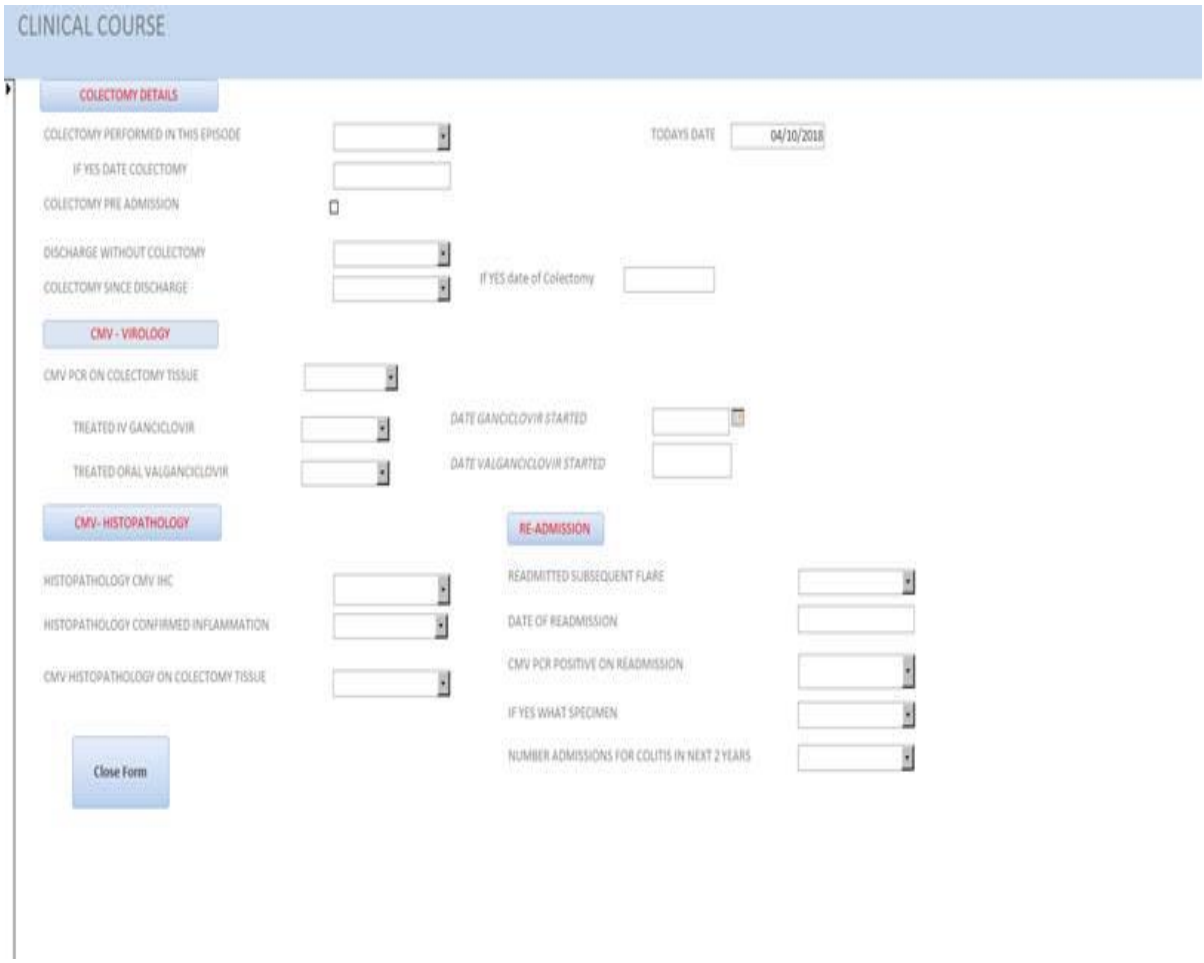
BASELINE CLINICAL TAB:



CLINICAL DATA INVESTIGATIONS TAB:



CLINICAL COURSE TAB;



The **Regulation** and
Quality Improvement
Authority

The Regulation and Quality Improvement Authority
9th Floor
Riverside Tower
5 Lanyon Place
BELFAST
BT1 3BT

Tel 028 9536 1111
Email info@rqia.org.uk
Web www.rqia.org.uk
@RQIANews